CATALYTIC OXIDATIVE CARBONYLATION OF AMINES USING TUNGSTEN CARBONYL COMPLEXES

By

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"How often have I said to you that when you have eliminated the impossible, whatever remains, *however improbable*, must be the truth?"

Sir Arthur Conan Doyle, *The Sign of Four*

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Abstract of Dissertation Presented to the Graduate School
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CATALYTIC OXIDATIVE CARBONYLATION OF AMINES USING TUNGSTEN CARBONYL COMPLEXES

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Major Department: Chemistry

Although transition metal-catalyzed carbonylation reactions have been investigated extensively over many years, carbonylation systems involving Group 6 metals still remain rare. This dissertation describes an example of carbonylation of amines using Group 6 metals in which reaction of the iodo-bridged tungsten(IV) carbonyl dimer $[(CO)_2W(NPh)I_2]_2$ with excess primary or secondary amines results in formation of carbonylation products. Secondary amines are selectively converted into formamides in moderate yields, while primary amines produce ureas in good to high yields.

Additionally, $[(CO)_2W(NPh)I_2]_2$ has been demonstrated to be a catalyst for the oxidative carbonylation of primary amines to 1,3-disubstituted ureas. The amine complexes $(CO)_2I_2W(NPh)(NH_2R)$ [R = *n*-Bu, R = *n*-Pr, R = *t*-Bu] and $[(CO)_2IW(NPh)(NH_2R)_2]^+$ [R = *n*-Bu, R = *n*-Pr] have been isolated from reactions of $[(CO)_2W(NPh)I_2]_2$ with primary amines. These amine complexes have been shown to lie along the pathway to the catalytically active species. A possible mechanistic pathway involving carbamoyl and isocyanate complexes has been proposed.

Furthermore, it has been determined that primary and secondary amines can be oxidatively carbonylated to 1,3-disubstituted and tetrasubstituted ureas, respectively, using

$W(CO)_6$ as catalyst and I_2 as the oxidant. Preparation of various N,N'-disubstituted ureas from aliphatic primary amines RNH_2 (R = *n*-Pr, *n*-Bu *i*-Pr, *sec*-Bu, and *t*-Bu) was achieved in good to high yields. In addition, preparation of the corresponding tetrasubstituted ureas from the aliphatic secondary amines HNR_2 (R = C_2H_5, *n*-Bu, *i*-Pr, $PhCH_2$) and HNRR' (R,R' = $-(CH_2)_4-$; $-(CH_2)_5-$; $PhCH_2$, CH_3) was achieved in moderate yields. Aromatic primary and secondary amines are unreactive.

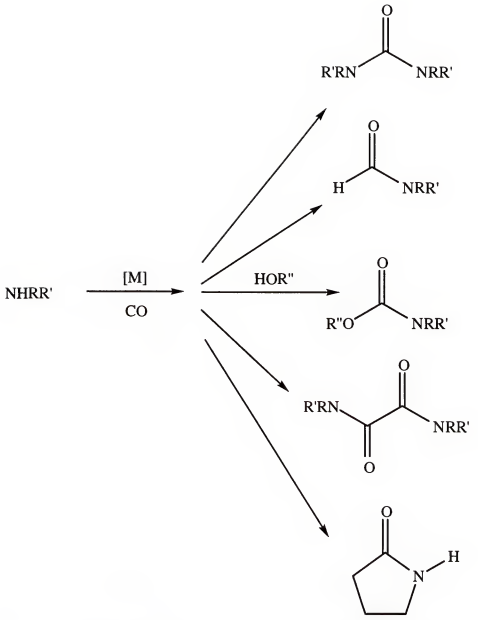
As an extension of the carbonylation system, primary and secondary diamines can be catalytically carbonylated to cyclic ureas using $W(CO)_6$ as the catalyst, I_2 as the oxidant, and CO as the carbonyl source. Preparation of five, six, and seven-membered cyclic ureas from the diamines $RNHCH_2(CH_2)_nCH_2NHR$ (n = 0 – 2; R = H, Me) and $RNHCH_2CH_2NHR$ (R = Et, *i*-Pr, Bz) was achieved in moderate to good yields. This is the first example of a viable method to carbonylate primary and secondary diamines to cyclic ureas.

CHAPTER 1
INTRODUCTION TO CARBONYLATION OF AMINES

Carbonylation of Amines

Carbonylation of amines is a topic of long standing interest.[1] In recent years, the oxidative carbonylation of amines in the presence of transition metal catalysts has attracted much attention due to the increased desire for new synthetic routes to ureas, carbamates, and isocyanate derivatives. Substituted ureas have a wide variety of applications, including agricultural additives, pharmaceuticals, and dyes.[2] Carbamates can be used as chiral auxiliaries, pharmaceuticals and isocyanate precursors.[3] In addition, isocyanates can be used as precursors for polyurethanes and polyureas.[4] The metal-catalyzed conversions of amines into ureas,[5] formamides,[6] carbamates,[7] α-keto amides,[8] and lactams[9] have been reported (**Scheme 1.1**).

The traditional method used to carbonylate amines involves phosgene.[10] However, phosgene is a highly toxic and corrosive gas, which upon reaction generates HCl. Interest in non-phosgene carbonylation methods has driven a great deal of research in recent years.[11] As a result, less hazardous methods have been developed over the last two decades, typically involving the catalytic carbonylation of organic molecules in the presence of transition metal complexes and carbon monoxide.[12]



Scheme 1.1 Carbonylation of amines in the presence of transition metal catalysts and carbon monoxide

Carbonylation of Amines In the Presence of Transition Metal Complexes

Original efforts

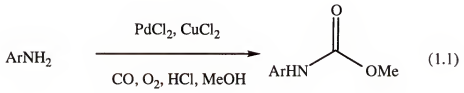
The original studies on the transition metal catalyzed carbonylation of amines, conducted in Germany during World War II, focused on nickel salts as catalysts.[5] Even though the metal was added as a salt or powder, the catalytically active species were undoubtedly metal carbonyls. Subsequent experiments established that amines react with carbon monoxide in the presence of catalytic amounts of metal carbonyls. These experiments also indicated that the carbonylation products, substituted ureas or N-formyl derivatives, depend both on the metal and the substrate. Subsequently, catalysts involving Pd,[5d,5f-g,7a-e,7g-j,8a-c,13] Ni,[5a] Co,[5c,6e,7f,9a] Rh,[12b,7g,9b] Fe,[14] Ru[5f,6a-d,6f,7g,15] Mn,[5b,5e-f] and Re[6g] were demonstrated to carry out this reaction. However, although many transition metal systems have been examined, carbonylation reactions involving Group 6 metals still remain rare.

Carbonylation of amines with group 10 metal complexes

Palladium is the transition metal most commonly used in catalysts for the carbonylation of amines. Initially, $PdCl_2$ was used to carbonylate both primary aliphatic and aromatic amines to isocyanates with carbon monoxide.[13] Using low pressures and temperatures, isocyanates are produced in low to moderate yields.

Interest in methods for phosgene-free isocyanate preparation has driven a great deal of work on the carbonylation of amines. The isocyanate targets are easily available by thermal elimination of alcohols from carbamates. Alper has reported that amines can be carbonylated to carbamates using $PdCl_2$ (eq 1.1).[7j] When aryl amines are reacted in the presence of a catalytic amount of $PdCl_2$ and $CuCl_2$ under a mixture of CO and O_2 in

methanol, methyl carbamates are produced in 16-99% yield, depending on the aryl group. Addition of HCl to the reaction mixture is also necessary to facilitate catalysis.



(1.1)

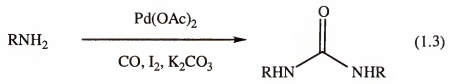
However, since mixtures of CO and O_2 are potentially explosive, less hazardous oxidants have been sought. Changing the oxidant to di-*tert*-butyl peroxide also leads to the carbonylation of primary aliphatic and aromatic amines to carbamate esters in good yields.[8c] Secondary amines undergo double carbonylation to oxamate esters, using either peroxide or oxygen.

Studies by Fukuoka revealed that carbamates can also be formed from amines using Pd black as a catalyst in the presence of CO, O_2, and an alkali metal.[7h,i] The addition of an alkali metal is especially important when the halide is iodide. As opposed to the other halides, iodide appears to be necessary for the reaction to proceed catalytically. Several iodide sources were examined and in the presence of each, Pd black catalyzed the carbonylation of aniline in ethanol to afford the carbamate in 85 - 95% yield.

Carbamates can also be synthesized from aromatic amines under very mild conditions utilizing indirect electrochemical carbonylation with $Pd(OAc)_2$ as the catalyst.[7c] As seen in equation 1.2, *p*-toluidine can be converted to methyl-N-*p*-tolylcarbamate in 85% yield. This innovative method can convert a variety of aromatic amines cleanly to carbamates in high yields, while also efficiently regenerating the catalyst system.

(1.2)

Both primary and secondary amines can be carbonylated to either ureas or oxamides in the presence of a catalytic amount of $Pd(OAc)_2$. Ureas are produced when I_2 is used as an oxidant and acetonitrile is the solvent (eq 1.3).[5d] However, oxamides are formed in high yields when secondary amines are carbonylated in the presence of iodide and O_2. Product yields are improved with the addition of a base, such as K_2CO_3, to prevent conversion of the amine to $RNH_3^+I^-$ by the HI byproduct.



(1.3)

When the solvent is an alcohol, carbamates are formed from the carbonylation of aromatic and aliphatic primary amines in the presence of a catalytic amount of $Pd(OAc)_2$. Carbonylation only occurs with the addition of an oxidant, either a stoichiometric amount of I_2 or a catalytic amount of I_2 in the presence of a mixture of CO and O_2.[7b] Schwartz has postulated that I_2 serves to convert the amine to an N-iodoamine, which undergoes oxidative addition to a low valent Pd species produced *in situ*. Further reactions of the resulting amide complex would then yield the carbamate.

Montmorillonite-bipyridinylpalladium(II)acetate (Pd-Clay) can also be used as a catalyst for the formation of carbamates from aliphatic, alicyclic, and/or aromatic mono-, di-, and triamines.[7a] This solid phase system, which runs under a mixture of CO and O_2 gases, is highly selective for carbamates and produces them in good to excellent yields, making it comparable to other homogenous palladium catalyzed carbonylation systems.

Another heterogeneous carbonylation system, Pd/C-NaI, has been used in the carbonylation of aniline to N,N'-diphenylurea, under a mixture of CO and O_2 gases at 170°C.[5g] In the presence of an alcohol, the carbamate is obtained. However the reaction is not catalytic and must occur at elevated temperatures.

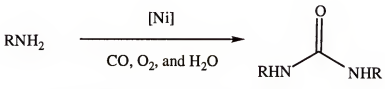
Furthermore, other palladium complexes such as PdI_2, $Pd(C_6H_5NH_2)Cl_2$, $PdCl_2(PPh_3)_2$ and $Pd(ppen)_2Cl_2$ can carbonylate primary aliphatic and aromatic amines to either ureas or carbamates, depending upon the reaction conditions. [5f,7d,g] Typically a form of iodide is used as a promoter and the reactions are run under a mixture of CO and O_2. Conversions and selectivity depend both on the catalyst and the reaction conditions. In addition, N,N'-disubstituted ureas and carbamates are also formed by the reaction of palladium complexes of the formula $[PdL_2Cl_{2-n}(OAc_3)_2]$ (n = 1 or 2; L_2 = chelating ligand) in the presence of $[RNH_3]Cl$ or $CuCl_2$. [7e]

Amides and α-keto amides can be formed from the reaction of methylpalladium carbamate or amide complexes under CO pressure (eq 1.4). [8a] These double and single carbonylation products are formed in good to moderate yields. In studying complexes as model intermediates for double carbonylation reactions, it was found that the reaction of trans-$[PdPh(acetone)(PMe_3)_2]PF_6$ with secondary amines, under atmospheric CO pressure, affords the corresponding amides and α-keto amides. [8b]

$$PdMe(OCONRR')(PMe_3)_2 + CO \longrightarrow MeCOCONRR' + MeCONRR' \qquad (1.4)$$

While the carbonylation of amines is most commonly catalyzed by palladium complexes, studies have been done on many nickel complexes, in search of a less expensive alternative. Nickel complexes have been known to react stoichiometrically with amines under CO pressure to produce oxamides. In an attempt to carry this reaction out catalytically, Giannoccaro reacted primary amines at 70° with a mixture of CO and O_2 in the presence of catalytic amounts of various nickel complexes, such as $Ni(BuNH_2)_4Cl_2$, $Ni(BuNH_2)_4Br_2$, $Ni(BuNH_2)_4I_2$, $Ni(PPh_3)_2I_2$, $Ni(BzNH_2)_4Br_2$, $Ni(BuNH_2)_6(ClO_4)_2$, and $NiCl_2$ (eq 1.5). [5a] Instead of the expected oxamide, N,N'-disubstituted ureas were produced in low yields. Investigation of the mechanism indicated that water played a significant role in product selectivity. Absence of water promotes oxamide formation,

while its presence promotes urea formation. The low yields can be attributed to the O_2 oxidant, which produces amine-N-oxides as side products.



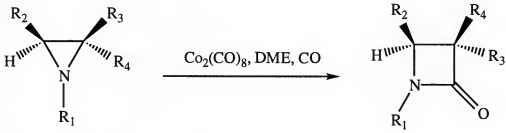
(1.5)

Carbonylation of amines with group 9 metal complexes

Secondary amines can be carbonylated to formamides using $Co_2(CO)_8$ as a catalyst.[6e] An early report by Sternberg describes the carbonylation of dimethylamine and piperidine catalyzed by $Co_2(CO)_8$, at 200°C and 200 atm CO. (eq 1.6) The corresponding formamides were obtained in yields of 60-78%.

(1.6)

In addition, $Co_2(CO)_8$ can be used to carbonylate aziridines to β-lactams under CO pressure.[9a] (eq 1.7) When non-activated 1,2-disubstituted aziridines are reacted in DME

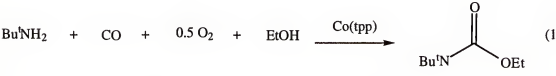


(1.7)

for 1 day at 100°C and at 33 atm CO, they undergo a carbonylative ring expansion to β-lactams in high yields with inversion of configuration. Cobalt tetracarbonyl anion is postulated to induce nucleophilic ring opening of the aziridine at the less substituted carbon, resulting in the inversion of configuration. This step is followed by CO insertion into the

Co-C bond, which proceeds with retention of configuration. Ring closure produces the β-lactam and regenerates the catalyst.

Metallomacrocyclic compounds of cobalt have been used as catalysts for the oxidative carbonylation of primary amines to carbamates (eq 1.8).[7f] Metalloporphyrins, metal Schiff bases, and phthalocyanines of cobalt can serve as catalysts for this reaction, when molecular oxygen is used as the oxidant. Iodide, added in the form of NaI, acts a promoter enhancing the rate of reaction. Unlike the reaction where $Co_2(CO)_8$ is used as a catalyst, formamides are not produced, even as side products. In other systems, formamides are likely to arise from the reductive elimination of a carbamoyl ligand and a metal hydride from cis coordination sites. The high selectivity achieved with metallomacrocyclic complexes may be attributed to their square planar coordination, which does not allow for *cis* coordination sites to be occupied by other ligands.



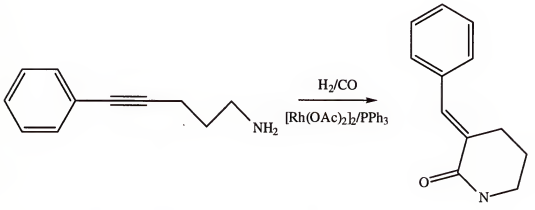
(1.8)

Treatment of certain aromatic primary amines in methanol with CO (1 atm) and O_2 (1 atm) in the presence of N,N-bis(salicylidene)ethylenediaminocobalt(II) as a catalyst produces both carbamates and ureas. The proposed intermediate is an organic isocyanate, which is expected to give low selectivity. However, subsequent systematic optimization studies were conducted until the selectivity for urea became quite high, and only small amounts of carbamates and azo derivatives were produced as side products.[5c]

Various rhodium complexes, such as $RhI_3 \cdot 3H_2O$ and $Rh(CO)_2(acac)$, have been shown to carbonylate aromatic amines to both carbamates and ureas, depending upon the reaction conditions.[7g] Iodide, either added to the reaction as NaI or attached to the metal as a ligand, acts as a promoter. Iodide increases both the activity of the catalysts and selectivity of the reaction for carbamates.

Other rhodium catalysts give mixtures of products. For example, the carbonylation of *n*-butylamine in the presence of $[Rh(CO)_2Cl]_2$ at 160°C and 60 bar affords a mixture of N-butylformamide and di-*n*-butylurea.[12b] On the other hand, when the reaction is carried out in the presence of PMe_3, N-butylformamide is formed in a quantitative yield.

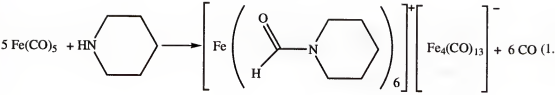
Rhodium catalysts have also been used to catalyze the carbonylation of acetylenic amines.[9b] When γ-aminoalkynes are reacted with H_2/CO in the presence of $[Rh(OAc)_2]_2/PPh_3$, substituted α-methylene lactams are produced as major products (eq 1.9). With arylalkynes the reaction is very stereo- and regioselective.



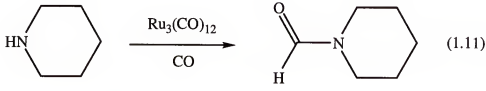
(1.9)

Carbonylation of amines with group 8 metal complexes

Carbonylation of secondary amines in the presence of iron carbonyl complexes produces formamides, but the reaction is not general (eq 1.10). Hieber and Kahlen have shown that $Fe(CO)_5$ reacts stoichiometrically with piperidine, morpholine, or dimethyl amine at room temperature to yield the corresponding formamides.[14] The same metal carbonyl also reacts with liquid ammonia at room temperature to form urea. However, the reaction is quite slow, only reaching completion after 15 days. In addition, both $Fe_2(CO)_9$ and $Fe_3(CO)_{12}$ react with liquid ammonia at room temperature to produce urea.



Formamides can be obtained using Ru carbonyl catalysts, but the reaction was not general. Rempel reported the carbonylation of cyclic secondary amines to formamides under mild conditions (75°C, 1 atm CO) using various ruthenium catalysts.[6f] Ruthenium complexes such as $[Ru(CO)_2(OAc)]_n$, $Ru(OAc)_2$ and $Ru_2(OAc)_4$, were capable of carbonylating amines to the N-formyl derivatives under a slight excess of CO pressure. However, $Ru_3(CO)_{12}$ was the most effective catalyst, converting piperidine to N-formyl piperidine in a 45% yield in 65 hours (eq 1.11). In addition, $Ru(CO)_2I_2$ can carbonylate ammonia to formamide at -30°.[15]



Although it is generally true that secondary amines are more easily and selectively converted to formamides than primary amines, $Ru_3(CO)_{12}$ was also demonstrated to catalyze the formation of formamides from primary amines when more forcing conditions were applied (180°, 39 atm).[6d] A carbamoyl species is suggested as a key intermediate in the catalysis. Either an intermolecular 1,2-shift reaction between a coordinated CO and an amine ligand or, more likely, the nucleophilic attack of an amine on a coordinated carbonyl ligand results in the formation of a carbamoyl complex. Due to insolubility problems, the carbamoyl species could not be isolated, however IR data is consistent with the formation of a carbamoyl ligand. Similar to other postulated mechanisms, formamides are proposed to form from the reductive elimination of a hydridocarbamoyl species.

In addition to $Ru_3(CO)_{12}$, other ruthenium cluster compounds such as $[HRu_3(CO)_{11}]^-$ and $[H_3Ru_4(CO)_{12}]^-$ have been found to catalyze the carbonylation of cyclic amines to formamides.[7a] The catalytic reaction works under both carbon monoxide and a mixture of hydrogen and carbon dioxide pressures. In addition, a neutral carbamoyl cluster complex was isolated from the reaction mixture, as a possible intermediate.

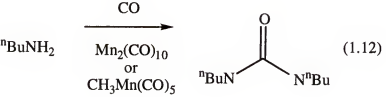
Amines can also be carbonylated in the presence of $RuCl_3H_2O$.[7b] However, stringent conditions (180°C, 80 atm CO) were required to obtain high turnovers. Additional work showed that $RuCl_3H_2O$ could also be used as a catalyst for the carbonylation of secondary amines, but only in the presence of methanol.[7c] Mechanistic studies on this reaction revealed that methanol was being converted to methyl formate which reacts with amines to yield formamides. In the absence of alcohols, $RuCl_3$-catalyzed reaction of acyclic amines lead to mixtures of formamides, ureas, and transalkylated amines.

Aniline can be carbonylated to either N,N-diphenylurea or N-phenyl-methylcarbamate in the presence of various ruthenium complexes, such as $Bu_4N[Ru(CO)_3I_3]$, $Ru(CO)_2(py)Cl_2$, and $Ru(CO)_3I_3$.[5f,7g] Conversion of aniline to the carbamate can be achieved in moderate yields with low selectivity at 170°C with a 13:1 mixture of CO and O_2 in methanol. Oxidative carbonylation of aniline to N,N'diphenylurea is achieved in moderate yields at 100°C with a mixture of CO and O_2 at atmospheric pressure conditions in DMF.

Carbonylation of amines with group 7 metal complexes

Calderazzo discovered that primary aliphatic amines could be converted into disubstituted ureas by the use of $Mn_2(CO)_{10}$ and $CH_3Mn(CO)_5$ (eq 1.12).[5e] While primary amines produce ureas exclusively, secondary and tertiary aliphatic amines remained

unreactive. However, diphenylurea was produced in very low yield from aniline. The reaction conditions are quite harsh, with 130 atm CO and between 180-200°C. In addition, very small amounts of the alkylformamide appear as a minor side product.



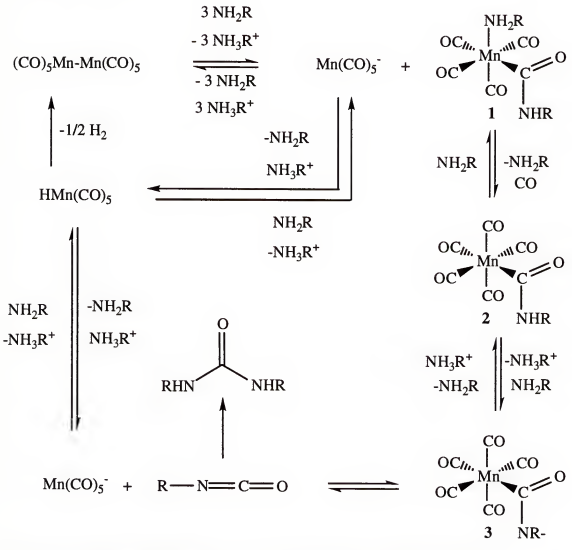
(1.12)

Following Calderazzo's original study, Dombek and Angelici conducted a mechanistic study involving the carbonylation of primary aliphatic amines to ureas catalyzed by $Mn_2(CO)_{10}$ and $CH_3Mn(CO)_5$.[5f] The primary diamine 1,3-diaminopropane reacted with the manganese catalysts, producing the six-membered cyclic urea in very low yields. However, a longer chain aliphatic diamine, 1,6-diaminohexane produced a polyurea.

During the course of the mechanistic study, several stoichiometric reactions were examined, in order to postulate the reaction mechanism depicted in **Scheme 1.2**. In this mechanism, the primary amine reacts with $Mn_2(CO)_{10}$ to produce the carbamoyl species **1**. Under excess CO pressure, a coordinated amine is replaced by a CO molecule, giving **2**. The now free amine then deprotonates the carbamoyl ligand producing **3**, which easily releases an organic isocyanate. Reaction of the free isocyanate with any excess amine would quickly give the disubstituted urea. $HMn(CO)_5$ is left as a reaction product, which then evolves H_2 to regenerate the binuclear catalyst, $Mn_2(CO)_{10}$. In addition, $HMn(CO)_5$ was found to also be an active catalyst for the reaction, probably catalyzing the reaction by a similar mechanism. However, it was found that $(CH_3C_5H_4)Mn(CO)_3$ was too inert to be converted to the catalytic form.

In contrast to Dombek and Angelici's results, Srivastava et al. found that $(CH_3C_5H_4)Mn(CO)_3$ can be used to produce urea.[5b] When $(CH_3C_5H_4)Mn(CO)_3$ is irradiated with UV light for 100-250 hours in the presence of a primary amine, the

disubstituted urea is formed in low to moderate yields. Unlike other metal complexes which facilitate the catalytic carbonylation of amines, $(CH_3C_5H_4)Mn(CO)_3$ acts as a stoichiometric reagent.

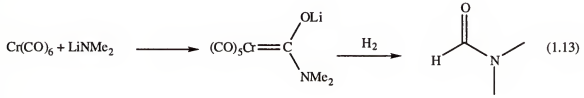


Scheme 1.2 Postulated mechanism for the carbonylation of primary amines catalyzed by $Mn_2(CO)_{10}$

Ammonia can be carbonylated to formamide by stoichiometric reaction with $Re(CO)_5Cl$.[68] This is one of the rare examples of carbonylation with a third row transition metal.

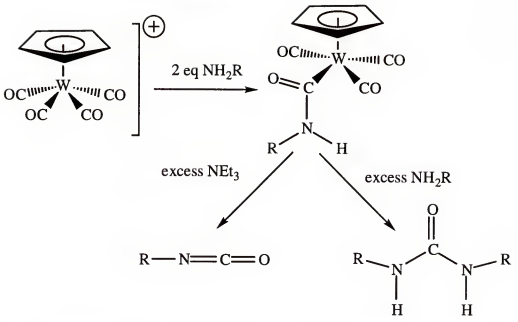
Carbonylation of amines with group 6 metal complexes

Although there has been a great deal of work on amine carbonylation reactions, cases involving Group 6 metals remain extremely rare. In one example, Grubbs reacted $Cr(CO)_6$ with $LiNMe_2$ to obtain the anionic carbamoyl complex $Li[(CO)_5CrCONMe_2]$.[16] Hydrogenation of this species at 130°C produced dimethylformamide in 15-35% yields (eq 1.13).



(1.13)

In a second example of carbonylation with a Group 6 metal, Angelici reported the formation of 1,3-dimethylurea upon reaction of $[(\eta^5\text{-}C_5H_5)M(CO)_4]PF_6$ (M = Mo, W) with excess CH_3NH_2 (**Scheme 1.3**).[17] In the presence of only two equivalents of amine, the carbamoyl complexes $(\eta^5\text{-}C_5H_5)M(CO)_3(CONHCH_3)$ were obtained, suggesting that the first step was nucleophilic attack on a carbonyl ligand. Further reaction of the carbamoyl complex with excess primary amine gave the corresponding N,N'-disubstituted urea, while reaction with excess triethylamine gave an organic isocyanate. Similar to the manganese case previously discussed, the authors postulate that the first equivalent of primary amine deprotonates the carbamoyl ligand producing an isocyanate, which then reacts with another equivalent of primary amine to yield the urea. The production of an organic isocyanate in the presence of a tertiary amine, which can only deprotonate the carbamoyl ligand, is further supporting evidence.



Scheme 1.3 Stoichiometric carbonylation of amines using a tungsten carbamoyl complex

Summary and Conclusions

Amines can be carbonylated to ureas, formamides, carbamates, α-keto amides, and lactams by various transition metal catalysts in the presence of carbon monoxide. This less hazardous method is a viable alternative to carbonylation with phosgene. While many transition metal systems have been extensively studied, carbonylation reactions involving Group 6 metals is extremely rare.

CHAPTER 2
CARBONYLATION OF AMINES WITH A TUNGSTEN(IV) CARBONYL DIMER

Background

Previously, the McElwee-White group reported the formation of the iodo-bridged dimer $[(CO)_2W(NPh)I_2]_2$ (**5**) upon oxidation of the zwitterion $(CO)_5WNPhNPhC(OMe)Ph$ (**4**) with one equiv of I_2.[18] As seen in **Scheme 2.1**, subsequent treatment of dimer **5** with excess two electron donor ligands resulted in the formation of mononuclear compounds of the type $(CO)_2I_2W(NPh)L$, where L = THF (**6**), CH_3CN (**7**), pyridine (**8**), NEt_3 (**9**), or 2,4,6-$Me_3C_6H_2NH_2$ (**10**).

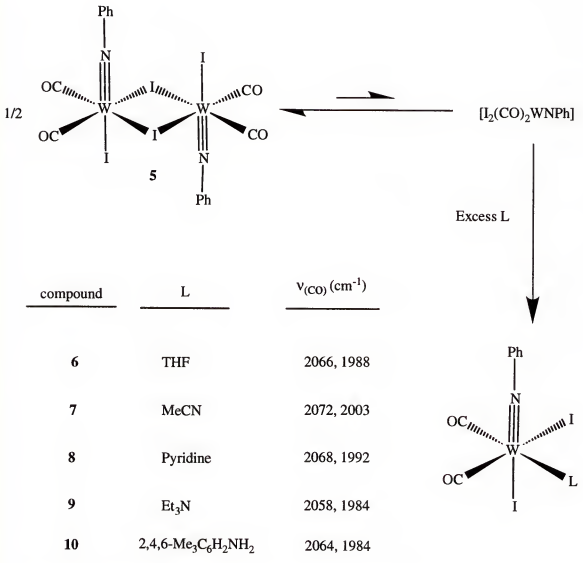
In an effort to extend the series of derivatives, **5** was reacted with excess secondary and primary aliphatic amines. However, upon treatment with either primary or secondary amines under nitrogen, a very complex reaction mixture resulted. Upon oxidation, amine carbonylation products were obtained.

Stoichiometric Carbonylation Reactions Using a Tungsten(IV) Carbonyl Dimer

Carbonylation of Secondary Amines to Formamides

Unlike the smooth conversions of **5** to several of the $(CO)_2I_2W(NPh)L$ compounds, treatment of a methylene chloride or THF solution of dimer **5** with 10 equiv of piperidine under nitrogen resulted in a very complex reaction mixture. After exposure to air, the solution turned from magenta to banana-yellow, producing 1-formylpiperidine, aniline, piperidine hydroiodide, and several unidentified components. GC analysis of the

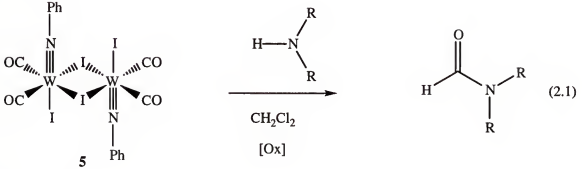
oxidized reaction mixtures established that 1-formylpiperidine had been obtained in 36% yield per equivalent of tungsten.



Scheme 2.1 Synthesis of a series of W(IV) imido complexes from **5**

Experiments with other secondary amines established that carbonylation to formamides using dimer **5** is a general reaction (eq 2.1). The results for a series of secondary amines are shown in **Table 2.1**. The GC yields, reported on a per tungsten basis, vary from 61% for pyrrolidine formamide to 8% for diethyl formamide. The low yield of diethyl formamide can be attributed to loss during the oxidation and work-up

procedures. Within the limits of detection, the carbonylation of secondary amines is selective for formamides. Despite literature precedent for formation of ureas and α-keto amides from amines, these species were not observed in the reaction mixtures.



Carbonylation of Primary Amines to Ureas

However, reaction of **5** with primary amines produced a different result. Under the same reaction conditions, primary amines were selectively carbonylated to the corresponding 1,3-disubstituted ureas (eq 2.2).

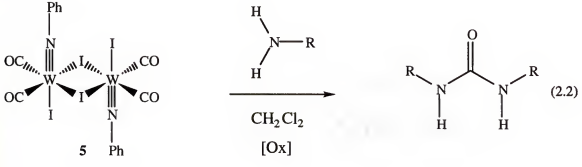
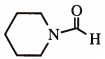
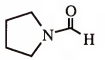
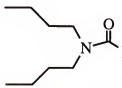


Table 2.1. Carbonylation of Secondary Amines to Formamides

Amine	Product	% Yield[a,b]
		36
		8
		61
		20

[a] calculated per equivalent of tungsten
[b] determined by GC

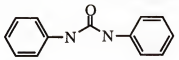
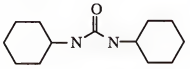
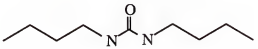
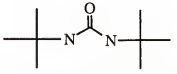
No other carbonylation products could be detected, although aniline and the amine hydroiodides could be observed in the ^{1}H NMR spectra of the reaction mixtures. The results for a series of primary amines are shown in **Table 2.2**. The isolated yields per tungsten vary from 56% for di-*n*-butylurea to 105% for diphenylurea. Since each tungsten has two carbonyls, the theoretical yield of urea is 200% if all the CO is consumed during the carbonylation reaction.

Carbonylation of Primary Diamines to Cyclic Ureas

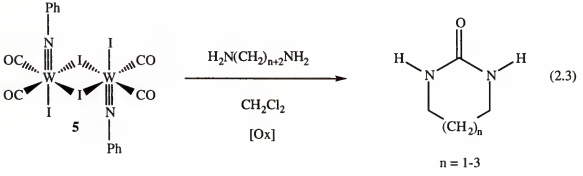
When **5** was reacted with α,ω-diamines under the stoichiometric oxidative carbonylation conditions, the diamines were converted to the corresponding cyclic ureas as

long as high dilution conditions were employed (eq 2.3). More concentrated solutions resulted in the formation of oligomers.[19]

Table 2.2. Carbonylation of Primary Amines to Ureas

Amine	Product	% Yield[a,b]
		105
		57
		56
		67

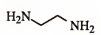
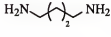
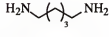
[a] calculated per equivalent of tungsten
[b] isolated yields



(2.3)

The results for a series of diamines are shown in **Table 2.3**. Closure of the five, six, seven, and eight membered cyclic ureas was achieved. The highest isolated yield (1.36 equiv of product per equiv of dimer **5**) was obtained for the six-membered cyclic urea, while only trace amounts of the eight-membered ring compound were formed.

Table 2.3. Stoichiometric Carbonylation of α,ω-Diamines to Cyclic Ureas.

Diamine	Urea	Yield[a,b]
		36%
		68%
		36%
		trace

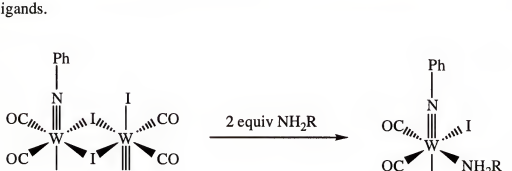
[a] Calculated per equiv of tungsten
[b] isolated yields

In summary, a method to stoichiometrically carbonylate primary and secondary amines using dimer **5** has been developed. This is a rare example of carbonylation using a Group 6 metal complex. The reaction not only proceeds under very mild conditions, but is selective as well. Primary amines produce ureas, while secondary amines yield formamides.

Mechanistic Considerations

Formation of Mononuclear Amine Complexes

In order to obtain mechanistic information about the carbonylation of primary amines by **5**, the necessary equivalents of amine were added in a stepwise manner. As shown in eq 2.4, reaction of **5** with two equiv of primary amine yielded the complexes $(CO)_2I_2W(NPh)(NH_2R)$ (**11**), in which the iodo-bridges of **5** have been replaced by amine ligands.

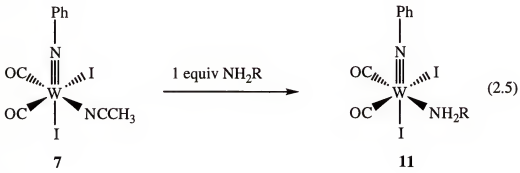


(2.4)

Similar conversions of **5** to mononuclear complexes by addition of two-electron donor ligands have been described previously.[18] Primary amine complexes derived from *n*-butylamine (**11a**), *n*-propylamine (**11b**), and *t*-butylamine (**11c**) were prepared, establishing that this is a general reaction. In addition, compounds **11a**, **11b**, and **11c** can also be generated by reacting the previously reported acetonitrile complex $(CO)_2I_2W(NPh)(NCCH_3)$ (**7**) with one equivalent of amine (eq 2.5).[18]

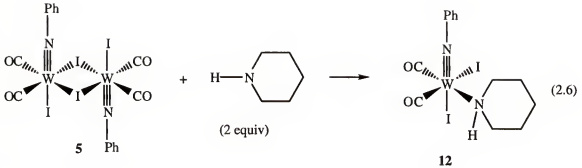
Amine complexes **11a-c** have been characterized by comparison of their spectral data to those of similar species.[18] The ^{1}H NMR spectra of **11a-c** reflect the chirality at the metal center. The diastereotopic NH_2 protons are seen as two broad singlets at 4.33 ppm and 4.02 ppm for **11a**, and 4.35 ppm and 4.03 ppm for **11b**, while for **11c** they appear

as two sets of doublets at 4.83 ppm and 4.07 ppm. The ^{13}C spectra of these complexes all exhibit two inequivalent carbonyl signals, which allow assignment of the carbonyl ligands as *cis*. Additional evidence for the stereochemistry at the metal can be found in the two IR stretches for the *cis*-carbonyl ligands.



7 **11** (2.5)

Similar to the reaction of **5** with two equiv of primary amines, reaction of **5** with two equiv of piperidine yielded $(CO)_2I_2W(NPh)(pip)$ (**12**) (eq 2.6). Complex **12** could be identified by comparison of its spectral data to those of similar complexes.[18] As observed with the THF and triethylamine adducts, the ^1H NMR spectrum of complex **12** reflects the chirality of the metal center. The β hydrogens of the piperidine ring are diastereotopic, appearing as well resolved quartets at 3.15 and 2.75 ppm. The NH proton is seen as a broad singlet at 4.34 ppm. The ^{13}C NMR spectrum of **12** exhibits two inequivalent carbonyl signals, which allows the assignment of the carbonyl ligands as *cis*. Additional evidence for the stereochemistry at the metal can be found in the two IR stretches for the *cis*-carbonyl ligands. Confirmation of the structural assignment was obtained by X-ray crystallography and a thermal ellipsoids drawing of **12** appears in **Figure 2.1**.



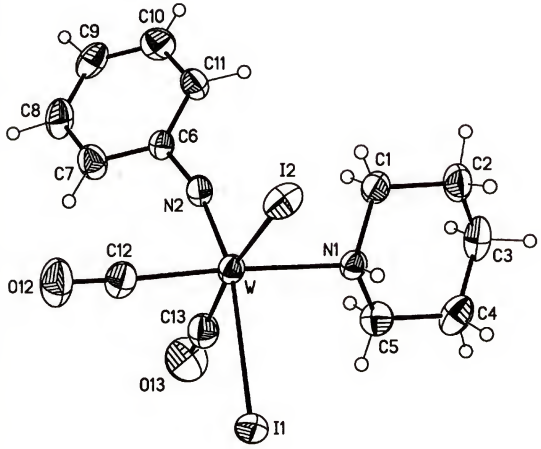
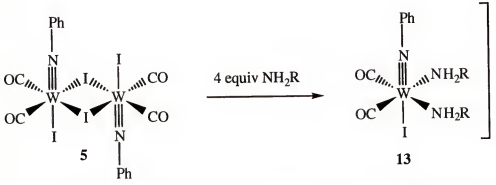


Figure 2.1 Thermal ellipsoids drawing of compound **12** showing the crystallographic numbering scheme. Thermal ellipsoids are drawn at the 40 % probability level. Selected distances (Å) and angles (deg) are as follows: W-N1 2.249(3), W-N2 1.764(3), W-C13 2.036(5), W-C12 2.053(4), W-I1 2.836(1), W-I2 2.794(1), W-N1-C1 111.7(2), W-N2-C6 164.9(3), N1-W-N2 100.6(1), C1-N1-C5 109.4(3).

Formation of Bis(amine) Cations

Reaction of **5** with four equiv of a primary amine produces the $[(CO)_2IW(NPh)(NH_2R)_2]^+$ complex **13** (eq 2.7), in which one of the iodide ligands of **11** has been replaced by an amine. The *n*-butylamine (**13a**) and *n*-propylamine derivatives (**13b**) have been successfully synthesized in this manner.



(2.7)

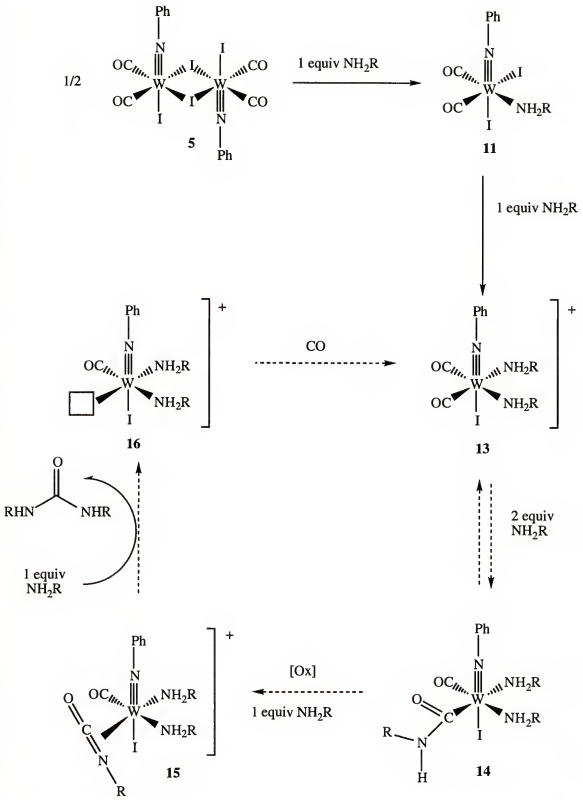
These bis(amine) cations are also available via reaction of **11a,b** with one equiv of the corresponding amine, or by addition of two equiv of amine to **7**. The ^1H NMR spectra of these complexes exhibit diastereotopic NH_2 protons at 5.4 ppm and 4.7 ppm for **13a** and at 5.2 and 4.9 ppm for **13b**. The ^{13}C spectra of these complexes each contain one carbonyl signal, as well as only one set of alkyl signals. The stereochemical assignment of the carbonyl ligands as *cis* derives from the two IR stretches at 2060 and 1989 cm^{-1} for both **13a** and **13b**.

The monomeric amine complexes were demonstrated to be on the reaction pathway by reaction of amine complexes **11a**, **11b**, and **11c** with excess amine under oxidative conditions. As expected, the corresponding 1,3-disubstituted ureas were produced. Similar experiments involving the cationic bis(amine) complexes **13a** and **13b** established that the reaction pathway was also accessible from these species. Attempts to isolate complexes further along the pathway by reaction of **5** with additional equivalents of amine proved to be unsuccessful.

Proposed Mechanism

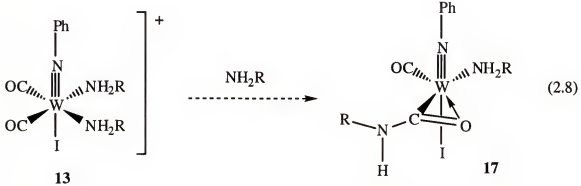
Although the remaining intermediates in the carbonylation process were too reactive to be characterized, literature precedent and the results of further experiments (*vide infra)* suggest the mechanism shown in **Scheme 2.2**. IR spectra of unoxidized reaction suggest the mechanism shown in **Scheme 2.2**. mixtures of **5** with *n*-butylamine exhibited a stretch at 1589 cm^{-1}, consistent with the presence of carbamoyl ligands.[20] Intermediacy of carbamoyl complex **14** (**Scheme 2.2**) or a related species is supported by Angelici's work on the carbonylation of CH_3NH_2 by $[(\eta^5\text{-}C_5H_5)W(CO)_4]PF_6$, for which the first step is conversion of $[(\eta^5\text{-}C_5H_5)W(CO)_4]^+$ to the carbamoyl complex $(\eta^5\text{-}C_5H_5)W(CO)_3(CONHCH_3)$ upon reaction with 2 equiv of CH_3NH_2. Formation of **14** from **13** would require an analogous nucleophilic attack of the amine on a carbonyl ligand, followed by deprotonation with a second equivalent of the amine. The carbonyl stretching frequency of 2066 cm^{-1} for **13** falls within the range where nucleophilic attack is expected to occur,[20n] rendering the conversion of **13** to **14** a reasonable possibility.

Given that the carbamoyl IR stretches disappear upon exposure of the reaction mixtures to air, the next step in the mechanism appears to be oxidation. Upon oxidation of the complex, the carbamoyl proton would become more acidic. Deprotonation of **14** by the excess amine would form an isocyanate complex such as **15**. Although isocyanates are likely intermediates in the carbonylation of amines by **5** and have been isolated from the reaction of Et_3N with $(\eta^5\text{-}C_5H_5)W(CO)_3(CONHCH_3)$,[17] no free or coordinated isocyanates have been detected in the reaction mixtures of amines with **5**. However, small amounts of isocyanates were observed in some of the reaction mixtures by GC. The GC evidence should be viewed with some skepticism since the observed isocyanates could arise from cracking of labile species in the injection port. However, their presence does provide some support for **Scheme 2.2**. Additionally, nucleophilic attack of an amine on either **15** or the free isocyanate to form the ureas would be expected to be facile.



Scheme 2.2 Proposed Mechanism

A less well-precedented mechanistic option is deprotonation of one of the amine ligands of **13**, followed by migratory insertion of the carbonyl into the tungsten-nitrogen bond. A similar sequence has been reported by Wang for a dicarbonyl rhenium cation bearing an amine tethered to a Cp ring.[21] In this system, deprotonation of the coordinated amine triggers CO insertion to produce an η^2-carbamoyl complex. Further addition of a two-electron donor ligand converts the carbamoyl to an η^1 configuration. Application of this sequence to amine complex **13** would produce η^2-carbamoyl complex **17** (eq 2.8). Addition of another equivalent of amine to **17** would produce intermediate **14**, at which point this route would converge with **Scheme 2.2**.



13 **17** (2.8)

The mechanism proposed in **Scheme 2.2** raised the interesting possibility that the reaction could be rendered catalytic in the presence of excess CO. As shown in **Scheme 2.2,** loss of isocyanate from **15** would yield the unsaturated intermediate **16**. Addition of CO to **16** would regenerate bis(amine) complex **13**, closing the catalytic cycle.

Catalytic Carbonylation Reactions Using a Tungsten(IV) Carbonyl Dimer

Catalytic Oxidative Carbonylation of Primary Amines to Ureas

The expectation that the catalytic cycle could be closed was confirmed by providing excess CO to the reaction mixture. For example, when **5**, 100 equiv of *n*-butylamine and 100 equiv of the oxidizing agent iodosylbenzene were placed in a 125-mL Parr high-pressure vessel and pressurized with 100 atm CO, di-*n*-butylurea was produced in an amount corresponding to 12 turnovers per equivalent of dimer **5** (**Table 2.4**). Since **5** is cleaved into mononuclear complexes in the presence of amines, each tungsten is turning over 6 times. However, since the tungsten was added to the reaction mixtures in the form of **5**, the yields are reported on this basis.

Table 2.4. Catalytic Carbonylation of *n*-Butylamine using Dimer **5**

Catalyst	Oxidant	TON[a]
5	I_2	15[b]
5	I_2	25[c]
5	PhIO	12[b]
5	Me_3NO	0.4[b]
5	t-BuOOH	1.2[b]
5	t-BuOO-t-Bu	1.2[b]
5	Ce(IV)	6[b]
5	$CuCl_2$	4[b]
5	air	1.2[d]

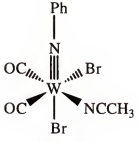
[a]Turnover number per equivalent of dimer **5**.
[b]Reaction conditions: amine (22 mmol), oxidizing agent (22 mmol), CO (100 atm), dimer **5** (0.22 mmol), room temperature, 24 h.
[c]Reaction conditions: amine (22 mmol), oxidizing agent (22 mmol), CO (100 atm), K_2CO_3 (22 mol), dimer **5** (0.22 mmol), room temperature, 24 h.
[d]Reaction conditions: amine (71 mmol), CO (800 psi), air (200 psi), dimer **5** (0.24 mmol), room temperature, 24 h.

Before catalytic reactions were studied further, effort was devoted to optimizing conditions for the stoichiometric reaction. Use of chlorinated solvents (CH_2Cl_2, $CHCl_3$ or CCl_4) resulted in the highest yields of product. Ureas were also formed in coordinating

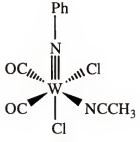
solvents such as acetonitrile and THF. However the yields were quite low, probably because these solvents compete with the amines for coordination sites. Since the starting dimer **5** is insoluble in most other common solvents, the range of usable solvents is limited.

The Effect of Iodide

The use of iodide complexes or the addition of iodine-containing promoters is common in the literature on oxidative carbonylation, especially in Pd-catalyzed reactions.[5d,7b,d,f-i] Since the role of the iodide ligands in the reactivity of **5** was unclear, a comparison of different halide ligands was carried out using complexes **7**, **18a**, and **18b**.[22] When iodide complex **7** was reacted with 10 equiv of *n*-butylamine under the stoichiometric conditions, 0.5 equiv di-*n*-butylurea was produced per equiv of **5**. In similar experiments, the bromide complex **18a** and the chloride complex **18b** were reacted with excess primary amines under the stoichiometric oxidative conditions. However, neither **18a** nor **18b** successfully formed ureas or any other detectable organic products, thus indicating that iodide ligands are necessary for the carbonylation reaction.



18a



18b

Examination of Oxidizing Agents

In efforts to determine the optimum conditions for catalytic conversion of primary amines to ureas, several oxidizing agents were examined (**Table 2.4**). Since iodide ligands facilitate the carbonylation reaction, I_2 was a reasonable choice as an oxidizing agent.[5d,7b,19] I_2 is the most effective oxidant examined, as measured by the number of catalyst turnovers. The addition of K_2CO_3 also proved to be important.[5d,7b,20] In the absence of added base, the turnovers are limited by the production of two equiv of the amine hydroiodide (RNH_3I) per equiv of urea. If the reaction is run in the presence of K_2CO_3, the amine salt byproduct can be recycled. Upon addition of K_2CO_3 to the I_2-oxidized reaction, di-*n*-butylurea was produced in an amount corresponding to 25 turnovers per equivalent of dimer **5** or 52% yield with respect to amine (**Table 2.4**).

Among the other oxidants that were examined, iodosylbenzene gave the best results of the oxo transfer reagents. Other oxo transfer reagents such as trimethylamine N-oxide also work but tend to be problematic when not extremely dry, since the carbonylation reaction is moisture sensitive. In the presence of water, yields of ureas are low. For this reason, hydrogen peroxide is a poor choice as oxidizing agent. Di-*t*-butylperoxide and *t*-butylhydroperoxide do induce carbonylation of amines by **5**, although multiple turnovers cannot be obtained and several unidentified side products are also formed. Outer sphere oxidants, such as Ce(IV) and $CuCl_2$ rendered the reaction catalytic as well. Since the original stoichiometric conditions utilized air as the oxidant, efforts were made to explore O_2 as the oxidant in the catalytic reaction. However, using a mixture of 800 psi CO and 200 psi air did not induce multiple catalyst turnovers, presumably because an intermediate species in the catalytic cycle is oxygen sensitive. For example, if the unsaturated complex **16** were to react with oxygen, the stoichiometric reaction would run in the presence of air as observed, but loss of **16** would prevent the reaction from turning over in the presence of O_2.

Summary and Conclusions

In summary, a rare example of carbonylation of amines with group 6 metals has been developed. The initial method to stoichiometrically carbonylate amines using dimer **5** was not only mild, but selective as well. Secondary amines produce formamides, while primary amines yield ureas. Furthermore, a possible mechanistic pathway involving carbamoyl and isocyanate complexes for the carbonylation of primary amines to ureas has been proposed. After elucidation of the mechanism, a mild method to catalytically carbonylate primary amines to ureas using dimer **5** as precatalyst and I_2 as the oxidant was successfully developed.

CHAPTER 3
CATALYTIC OXIDATIVE CARBONYLATION OF PRIMARY AND SECONDARY AMINES WITH $W(CO)_6$

Background

Substituted ureas have found widespread use as agricultural chemicals, pharmaceuticals, resin precursors, dyes, and additives to petroleum compounds and polymers.[2] Among the numerous methods for synthesis of N,N-disubstituted ureas are the reactions of primary amines with isocyanates, phosgene, or phosgene derivatives.[23] While reports describing the synthesis of disubstituted ureas are prevalent, methods for the synthesis of tetrasubstituted ureas are less common due to the difficulty of converting secondary amines directly to tetrasubstituted.[24] The best known method involves the reaction of a carbamoyl chloride with a secondary amine.[25] However both experimental[24] and safety[23] problems with this method have been noted. Tetrasubstituted ureas can also be obtained in good yields by the reaction of lithium amides with carbon monoxide, followed by oxidation.[26] In addition, tetrasubstituted ureas have more recently been produced from reaction of phosgene derivatives, such as 1,1-carbonylbisbenzotriazole[24] and N,N'carbonyldiimidazole (CDI)[27] with secondary amines.

Since phosgene is highly toxic and corrosive and phosgene derivatives can be expensive to use on a large scale, there is continuing interest in the development alternative systems for the synthesis of substituted ureas. This interest has led to exploration of the metal-catalyzed carbonylation of amines.[12] Transition metal catalysts involving Ni,[5a] Co,[5c] Mn,[5e,f] Ru[5g] and, most commonly, Pd[5d,h,19] have been demonstrated to carry oxidative carbonylation of primary amines to disubstituted ureas. However, the metal-catalyzed

reactions generally require high temperatures and pressures. In addition, yields for aliphatic amines are generally lower than those for aromatic cases. Main group elements such as sulfur[28] and selenium[29] can also serve as catalysts.

While transition metal catalyzed carbonylation of aliphatic and aromatic primary amines to 1,3-disubstituted ureas is well known, the direct carbonylation of secondary amines to tetrasubstituted ureas is less explored. Typically, transition metal catalyzed carbonylation of secondary amines selectively produces formamides.[6] However, there is one example of direct carbonylation of secondary amines and CO to tetrasubstituted ureas which involves $Pd(OAc)_2$ as the catalyst, iodine as an oxidant.[5d] Using this system, Alper converted several secondary amines to the corresponding tetrasubstituted ureas in yields that range from 67% for 1,3-dibenzyl-1,-dimethylurea to 2% for 1,1,3,3-tetrabutylurea.

Catalytic Oxidative Carbonylation of Primary Amines Catalyzed by $W(CO)_6$

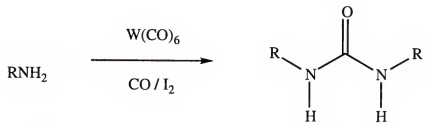
Although many transition metal systems have been examined, carbonylation of amines involving Group 6 metals[17] still remained rare. While carbonylation by **5** was the first successful example of catalytic amine carbonylation by a Group 6 metal, several problems were associated with the catalyst. Not only is **5** difficult and expensive to synthesize, but it is also heat, light, moisture and oxygen sensitive. In addition, ureas were produced in only moderate yields and many unidentifiable side products were present in the reaction mixtures. However, catalysis of amine carbonylation by **5** suggested that other Group 6 metal complexes could possibly serve as more efficient catalysts.

After considering the mechanism proposed in **Scheme 2.2**, it becomes evident that the imido ligand does not play a significant role in the reaction, serving only as a spectator ligand. Therefore, the only major requirements of the carbonylation reaction are a tungsten carbonyl compound, iodine, amine, oxidant, and carbon monoxide. The simplest tungsten carbonyl compound which could serve as precatalyst was the readily available,

inexpensive, and air stable $W(CO)_6$. However, conventional wisdom suggests that Group 6 metal complexes are poor carbonylation catalysts.[30]

Initial control experiments for the catalytic carbonylation of *n*-butylamine were carried out using $W(CO)_6$ as catalyst, without an oxidant. As expected, when $W(CO)_6$ and 50 equiv of *n*-butylamine are placed in a 125-mL Parr high-pressure vessel and pressurized with 100 atm CO, no di-*n*-butylurea is produced.

The fact that $W(CO)_6$ did not carbonylate amines to ureas was not too surprising. Based on the chemistry developed with **5**, the addition of an oxidant is necessary to induce carbonylation. The simple choice of oxidant is iodine, which would also serve as the source of iodide in the reaction. As seen in equation 3.1, when $W(CO)_6$, 50 equiv of *n*-butylamine and 25 equiv of iodine are placed in a 125-mL Parr high-pressure vessel and pressurized with 100 atm CO, di-*n*-butylurea is produced in an amount corresponding to 9 turnovers per equivalent of $W(CO)_6$ or a 33% yield based on amine (**Table 3.1**).



(3.1)

As observed in experiments involving dimer **5**, oxidative carbonylation of amines to ureas produces two equiv of amine hydroiodide salt per equiv of urea. Once again, addition of K_2CO_3 to release the free amine from the salt increases the turnover number dramatically. Reaction of $W(CO)_6$, 100 equiv of *n*-butylamine, 50 equiv of iodine, and 100 equiv K_2CO_3 in a 125-mL Parr high-pressure vessel pressurized with 100 atm CO produces di-*n*-butylurea in an amount corresponding to 39 turnovers per equiv of $W(CO)_6$ or 80% yield with respect to amine (**Table 3.1**).

Table 3.1. Catalytic Carbonylation of *n*-Butylamine using $W(CO)_6$

Catalyst	equiv n-$BuNH_2$	equiv I_2	equiv K_2CO_3	Time (h)	TON[a,b]
$W(CO)_6$	50	0	0	24	0
$W(CO)_6$	50	25	0	0.5	3
$W(CO)_6$	50	25	0	3	9
$W(CO)_6$	50	25	0	24	9
$W(CO)_6$	50	25	50	24	15
$W(CO)_6$	100	50	100	24	39

[a]Turnover number per equivalent of $W(CO)_6$.
[b]Reaction conditions: CO (100 atm), $W(CO)_6$ (0.21 mmol), room temperature.

Additional control experiments included addition of I_2 in only a trace amount. Since the reaction was starved for oxidant, only a trace amount of urea was formed. The potential participation of the stainless steel walls of the reactor was probed by control experiments using a glass liner. The number of turnovers obtained in the presence and absence of the glass liner did not differ significantly. Furthermore, the control experiment in which no catalyst was added but the solution was allowed to contact the stainless steel walls of the reactor was also performed. A negligible amount of urea was detected, but the amount was not significant with respect to the quantities of urea obtained in the presence of the catalyst.

Changing the precatalyst for amine carbonylation from **5** to $W(CO)_6$ is extremely significant. Dimer **5** is a heat, light, moisture, and oxygen sensitive compound that is expensive and time consuming to synthesize, while $W(CO)_6$ is a simple, stable, and inexpensive precatalyst which can be purchased from Aldrich. Amine carbonylation catalyzed by $W(CO)_6$ now becomes a viable synthetic method for the bulk preparation of ureas.

Optimization Experiments

Initially, the $W(CO)_6$ oxidative carbonylation system successfully carbonylated simple aliphatic primary amines to 1,3-disubstituted ureas in fairly good yields. However, the system was explored to see if altering reaction conditions could improve yields. Variables such as catalyst, temperature, addition of excess K_2CO_3, solvent, and CO pressure were examined.

As seen in **Table 3.2**, the initial reaction of 50 equiv of *n*-propylamine, in the presence of 2 mole % $W(CO)_6$, 25 equiv of iodine, and 50 equiv K_2CO_3 in 40 mL CH_2Cl_2 in a 125-mL Parr high-pressure vessel pressurized with 100 atm CO and stirred at room temperature for 18 hours produced di-*n*-propylurea in a 67% yield, with respect to amine. Since $W(CO)_6$ successfully carbonylated amines, the analogous other Group 6 metal carbonyl compounds, $Mo(CO)_6$ and $Cr(CO)_6$, were examined as catalysts.

Table 3.2. Catalytic Carbonylation of *n*-Propylamine with Group 6 Metals

Catalyst	% Yield[a,b]
$W(CO)_6$	67
$Mo(CO)_6$	50
$Cr(CO)_6$	30

[a] Isolated yield of 1,3-di-*n*-propylurea calculated per equiv of *n*-propylamine
[b] Reaction conditions: *n*-propylamine (14.2 mmol), catalyst (0.28 mmol), I_2 (7.1 mmol), K_2CO_3 (14.2 mmol), solvent (40 mL), room temperature, pressure 80 atm, 18 h.

Using $Mo(CO)_6$ as the catalyst, di-*n*-propylurea was produced in a 50% yield, while with $Cr(CO)_6$ the urea yield decreased further to 30%. It was expected that $Mo(CO)_6$ would be a more active catalyst than $W(CO)_6$, but it is possible that the molybdenum intermediates were too unstable under these reaction conditions. Even though third row transition metals are typically less active catalysts than the first or second row transition metals, $W(CO)_6$ appeared to be the better catalyst for the reaction.

Attempts to use less catalyst, only 1 mole % $W(CO)_6$, caused the carbonylation reaction to not reach completion lowering the urea yield to 54%. As seen in **Table 3.3**, a higher catalyst concentration, 2 mole % $W(CO)_6$ was necessary. Furthermore, increasing the temperature from room temperature to 90°C improved the yield an additional 5%.

Table 3.3 The Effects of Temperature and Excess K_2CO_3 on the Catalytic Carbonylation of *n*-Propylamine

Catalyst	equiv n-$PrNH_2$	equiv I_2	equiv K_2CO_3	Temp (°C)	% yield[a]
$W(CO)_6$	100	50	100	24	54
$W(CO)_6$	50	25	50	24	67
$W(CO)_6$	50	25	50	90	72
$W(CO)_6$	50	25	75	90	91
$W(CO)_6$	50	25	100	90	31
$W(CO)_6$	50	25	50	110	55

[a] Isolated yields calculated per equivalent of starting amine

The addition of 75 equiv of K_2CO_3 (1.5 with respect to amine) raised the yield to 91%. However, doubling the amount of base caused the yield to decrease to 31%. This can be attributed to stirring problems caused by the addition of the insoluble solid. Further raising the temperature to 110° C caused a decrease in yield to 55%. Since the resulting solution from this reaction was a brown oil, it is likely that the intermediates are not stable at or above this temperature.

After encountering insolubility problems with several amine substrates, such as cylclohexylamine and various *p*-substituted-benzylamines or their respective hydroiodide amine salts, a series of different solvents was examined, as seen in **Table 3.4**. Polar organic solvents such as CH_2Cl_2, $CHCl_3$, toluene, and ethyl acetate gave the best yields, as well as the cleanest crude products. The highest yield of di-*n*-propylurea at 62% was

formed with CH_2Cl_2 as the solvent. The remainder of the solvents examined, which are either non-polar or coordinating, gave urea yields under 40%. However, surprisingly, changing the solvent to methanol resulted in a change in the carbonylation product. In the presence of methanol, primary amines were carbonylated to formamides, instead of the expected ureas or carbamates.

Table 3.4. Comparison of Solvents in the Oxidative Carbonylation of *n*-Propylamine

Solvent	% Yield of Urea[a]
CH_2Cl_2	62
$CHCl_3$	51
Toluene	48
Ethyl Acetate	43
THF	41
CH_3CN	36
Ether	32
Water	32
CCl_4	28
Hexane	15
Acetone	14
Benzene	12

[a]Reaction conditions: amine (14.2 mmol), $W(CO)_6$ (0.28 mmol), I_2 (7.1 mmol), $K_2(CO)_3$ (21.3 mmol), solvent 40 mL, room temperature, pressure 80 atm, 24 h.

In attempt to conduct the carbonylation reaction under less CO pressure, a series of pressure experiments at 90°C was performed, as seen in **Table 3.5**. At 20 atm, the yield of di-*n*-propylurea was 63%, while at 90 atm the urea yield was 91%. Respectable yields can be achieved at lower pressures, however, high pressures are required to reach its maximum yield.

Table 3.5. Comparison of CO Pressure in the Oxidative Carbonylation of *n*-Propylamine

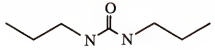
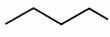
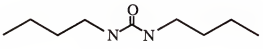
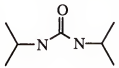
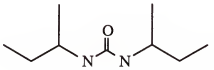
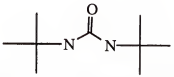
Pressure (atm)	% Yield of Urea[a]
20	63
40	68
60	75
80	91

[a]Reaction conditions: amine (14.2 mmol), $W(CO)_6$ (0.28 mmol), I_2 (7.1 mmol), $K_2(CO)_3$ (21.3 mmol), solvent 40 mL, room temperature, 24 h.

The best overall conditions were determined to be 2 mole% $W(CO)_6$, stoichiometric amounts of amine and I_2, 1.5 equiv of K_2CO_3 per equiv amine reacted at 90° C under 80 atm CO pressure in CH_2Cl_2. Under these conditions a series of several primary amines was reacted to give the corresponding N,N'-disubstituted ureas, as seen in **Table 3.6**. The ureas were formed in good to high yields, ranging from 91% for N,N'-di-*n*-propylurea to 53% for N,N'-di-*sec*-butylurea. The yields typically decrease with increasing steric bulk. It is noteworthy that aniline, an aromatic primary amine, remained unreactive under the reaction conditions, not producing the expected N,N'-diphenylurea.

In summary, aliphatic primary amines can be catalytically carbonylated to 1,3-disubstituted ureas in good to high yields using $W(CO)_6$ as the catalyst. The catalyst is commercially available, inexpensive and air stable, in contrast to dimer **5**. While the yields using this system are comparable with other transition metal catalysts, this system is both less toxic and less expensive. The urea yields are also similar to those resulting from carbonylation using traditional organic methods, however this system avoids phosgenation.

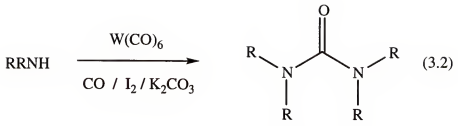
Table 3.6. Carbonylation of Primary Amines to Ureas

Amine	Product	% Yield[a,b]
		91
		84
		53
		55
		72

[a] calculated per equivalent of amine
[b] isolated yields

Catalytic Oxidative Carbonylation of Secondary Amines Catalyzed by $W(CO)_6$

Based on the similarity of the oxidation chemistry of primary amines with **5** and with $W(CO)_6$ / I_2, the reaction of secondary amines with CO in the presence of $W(CO)_6$ / I_2 was expected to produce formamides. However, as seen in equation 3.2, when $W(CO)_6$, 50 equiv of piperidine, 25 equiv of iodine, and 50 equiv K_2CO_3 are placed in a 125-mL Parr high-pressure vessel and pressurized with 80 atm CO, dipiperidylurea is produced in 36% yield based on amine (**Table 3.7**). The expected piperidine formamide was found in the reaction mixture in trace quantities as a side product.



(3.2)

Optimization Experiments

The yield of the dipiperidylurea from piperidine under these conditions was moderate. However, prior optimization for the oxidative carbonylation of primary amines to disubstituted ureas had results that ranged up to 91%. Based on the prior optimization of the primary amine cases, optimization studies were carried out using piperidine as a test case for secondary amines. Piperidine was chosen in part for comparison because several literature carbonylation studies have utilized piperidine.[7b, 6a-b] In addition, piperidine is a highly challenging substrate because its high basicity renders deprotonation of the byproduct amine salt problematic (vide infra).

Initial experiments involved comparison of $W(CO)_6$ to other Group 6 metal carbonyl compounds (**Table 3.7**). Although first and second row transition metals are generally more reactive than their third row congeners, $Mo(CO)_6$ and $Cr(CO)_6$ produced the tetrasubstituted urea in lower yields than those obtained with $W(CO)_6$. As seen in **Table 3.7**, when $Mo(CO)_6$ is used as the catalyst, dipiperidylurea was produced in a 19% yield, while with $Cr(CO)_6$ the urea yield was decreased further to 16%. Further optimization experiments were carried out only with $W(CO)_6$.

Table 3.7. Catalytic Carbonylation of Piperidine with Group 6 Metal Carbonyls

Catalyst	Yield[a] (%)
$W(CO)_6$	36
$Mo(CO)_6$	19
$Cr(CO)_6$	16

[a] Isolated yield of dipiperidylurea calculated per equivalent of piperidine
[b.] Reaction conditions: piperidine (14.2 mmol), $W(CO)_6$ (0.28 mmol), I_2 (7.1 mol), K_2CO_3 (14.2 mmol), solvent (40 mL), room temperature, pressure 80 atm, 18 h.

The results of variation of CO pressure are presented in **Table 3.8**. Although yields of disubstituted ureas from primary amines are dependent on the CO pressure, yields of dipiperidylurea vary little with CO pressure. At 40 atm, the yield of dipiperidylurea was 24%. As the total pressure varies from 40 to 90 atm, the yields only vary from 24% to 36%, with maximum value obtained at 60 atm.

Table 3.8 Comparison of CO Pressure in the Oxidative Carbonylation of Piperidine

Pressure (atm)	Yield (%)[a,b]
40	24
60	36
80	29
90	32

[a] Isolated yield of dipiperidylurea calculated per equivalent of piperidine
[b.] Reaction conditions: piperidine (14.2 mmol), $W(CO)_6$ (0.28 mmol), I_2 (7.1 mol), K_2CO_3 (14.2 mmol), solvent (40 mL), room temperature, 18 h.

Oxidative carbonylation of piperidine is also surprisingly unresponsive to changes in solvent, as seen in **Table 3.9**. Trial solvents were limited to those that had worked

well in the carbonylation of primary amines. Of the solvents examines, yields were highest with THF, but not significantly better toluene or CH_2Cl_2. The addition of water to the reaction does not affect the yield, as indicated when the reaction is run with a mixed solvent system of 35:5 mL CH_2Cl_2 / water. While acetonitrile is the solvent of choice in the $Pd(OAc)_2$-catalyzed system,[7b] with $W(CO)_6$ the yield is lowered to 8%, mostly due to the high affinity of acetonitrile for coordination to tungsten compounds.

Table 3.9. Solvent Effects in the Oxidative Carbonylation of Piperidine

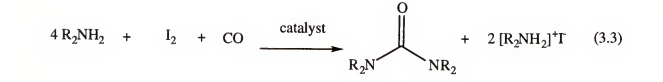
Solvent	Yield (%)[a,b]
THF	37
Toluene	31
CH_2Cl_2	29
CH_2Cl_2/Water[c]	29
CH_3CN	6

[a] Isolated yield of dipiperidylurea calculated per equivalent of piperidine
[b] Reaction conditions: amine (14.2 mmol), $W(CO)_6$ (0.28 mmol), I_2 (7.1 mmol), K_2CO_3 (21.3 mmol), solvent (40 mL), room temperature, pressure 80 atm, 15 h.
[c] CH_2Cl_2 (40 mL), Water (5 mL)

The stoichiometry of oxidative carbonylation of amines to ureas dictates that two equiv of the amine hydroiodide (R_2NH_2I) will be produced per equiv of urea (eq 3.3). Observation of piperidine hydroiodide in the reaction mixtures is consistent with this proton transfer. In the absence of added base, consumption of the amine substrate as a proton scavenger will thus limit the yields of urea. If the reaction is run in the presence of a sacrificial base, release of the free amine from the salt should increase the product yield.

The effects of different bases on the carbonylation of piperidine are presented in **Table 3.10**. When the reaction is run in the absence of a base the yield of urea is 33%, corresponding to 9 turnovers of the catalyst. However, the addition of 50, 75, or 100

equiv of K_2CO_3 to the I_2-oxidized reaction had virtually no effect on the yields. The similar yields of urea when the reaction is conducted in the absence or presence of base indicated that the K_2CO_3 was not deprotonating the amine salt, as does the detection of piperidine hydroiodide in the reaction mixture. The possibility that the deprotonation was not occurring due to the insolubility of K_2CO_3 in methylene chloride was eliminated when the reaction was run in a 35:5 mL mixture of methylene chloride / water and the yield remained the same (29%).



(3.3)

Since accurate pK_as in organic solvents are difficult to obtain, an empirical study of several other bases was carried out. When Na_3PO_4 was used as the base with CH_2Cl_2 as solvent, the dipiperidylurea was produced in a 36% yield, while in the CH_2Cl_2 / H_2O solvent mixture only a 4% yield of the urea was obtained. This indicates that Na_3PO_4 was also not deprotonating the amine hydroiodide salt in CH_2Cl_2. In the mixture with water, hydroxide generated by reaction with Na_3PO_4 was probably interfering with the carbonylation chemistry. While hydroxide is a strong enough base to deprotonate the amine salt, it is also nucleophilic and known to react with metal carbonyls. Problems with hydroxide in this system were corroborated by experiments with added hydroxide bases. For example, using KOH as the base, the urea was produced in only 8% yield in CH_2Cl_2 and in 3% yield in CH_2Cl_2 / water solvent mixture.

Nitrogen-containing bases which would not be substrates for the reaction, such as pyridine, NEt_3, and DBU were also examined. When pyridine was used as the base, the urea was produced in a 29% yield. However, when NEt_3 and DBU were used as bases, no urea was produced. Interestingly, addition of NEt_3 caused a shift in the reaction

chemistry. The only identifiable organic product from the NEt_3 study was N-formylpiperidine, which was formed in trace quantities.

Table 3.10. The Effects of Base on the Catalytic Carbonylation of Piperidine

Catalyst	Base	equiv	Solvent[c]	% yield[a,b]
$W(CO)_6$	K_2CO_3	0	CH_2Cl_2	33
$W(CO)_6$	K_2CO_3	50	CH_2Cl_2	36
$W(CO)_6$	K_2CO_3	50	CH_2Cl_2 / H_2O	29
$W(CO)_6$	K_2CO_3	75	CH_2Cl_2	29
$W(CO)_6$	K_2CO_3	100	CH_2Cl_2	32
$W(CO)_6$	KOH	50	CH_2Cl_2	8
$W(CO)_6$	KOH	50	CH_2Cl_2 / H_2O	3
$W(CO)_6$	Na_3PO_4	50	CH_2Cl_2	36
$W(CO)_6$	Na_3PO_4	50	CH_2Cl_2 / H_2O	4
$W(CO)_6$	Pyridine	50	CH_2Cl_2	29
$W(CO)_6$	NEt_3	50	CH_2Cl_2	0%
$W(CO)_6$	DBU	50	CH_2Cl_2	0%

[a] Isolated yield of dipiperidylurea calculated per equivalent of piperidine
[b] Reaction conditions: amine (14.2 mmol), $W(CO)_6$ (0.28 mmol), I_2 (7.1 mmol), room temperature, 80 atm CO, 15 h.
[c] CH_2Cl_2 (40 mL) or CH_2Cl_2 (40 mL) + water (5 mL)

Even though several different bases were examined, the turnover numbers did not exceed 9, which corresponds to an approximately 33% yield of urea. This is consistent with the reaction stoichiometry of two deprotonations per urea formed (eq 3.3) so that half of the amine is consumed as a base. Piperidine hydroiodide is also present in the reaction mixtures. The reaction thus appears to be limited by the inability of the bases to deprotonate the amine salt and return amine to the substrate pool. The choice of base for

this reaction is complicated by the fact that the metal carbonyl catalyst is vulnerable to nucleophilic attack. The base not only needs to be strong enough to deprotonate the HI salts of secondary amines, but it also needs to be non-nucleophilic. Unlike the reaction of primary amines, in which K_2CO_3 is adequate as the base, a suitable choice for the reaction of secondary amines has not yet been determined.

Further optimization experiments addressed other variables. Raising the temperature, which worked very well in the primary amine case, was ineffective. At 90 °C the yield of urea was lowered to 18%. Further increasing the catalyst concentration to 5 mole % gave a urea yield of 37%. The similar result with 2 mole % indicates that catalyst decomposition is not responsible for the low turnover numbers, consistent with the limiting factor being formation of the amine salt. In addition, longer reaction times (30 h) also did not result in any increase in urea yield.

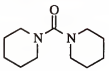
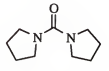
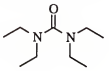
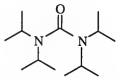
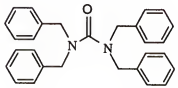
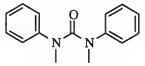
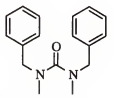
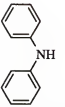
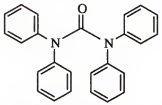
The best overall reactant ratios were determined from the piperidine optimization experiments to be 2 mole % $W(CO)_6$, equimolar amounts of K_2CO_3 and amine and 0.5 equiv I_2. The reaction was best carried out at room temperature under 80 atm CO pressure in CH_2Cl_2. Under these conditions several secondary amines were reacted to give the corresponding tetrasubstituted ureas, as seen in **Table 3.11**. The ureas were formed in moderate to good yields, ranging up to 55% for tetrabenzylurea. The yields typically decrease with increasing steric bulk, with diisopropylamine failing as a substrate. In addition, as observed for the carbonylation of primary amines under these conditions, aromatic amines do not react.

Summary and Conclusions

In conclusion, both primary and secondary amines can be catalytically carbonylated to ureas using the newly developed $W(CO)_6$ / I_2 system. 1,3-disubstitutedreas can be synthesized from primary amines in good to high yields, while tetrasubstituted ureas can be

formed from secondary amines in moderate to good yields. Although no mechanistic studies have been carried out, the reaction may follow a cycle similar to that proposed in **Scheme 2.2** for the chemistry of dimer **5**.

Table 3.11 Carbonylation of Secondary Amines to Ureas

Amine	Product	% Yield[a,b]
		36
		33
		40
		0
		55
		0
		49
		0

[a] Isolated yield of urea calculated per equivalent of amine

[b] Reaction conditions: amine (14.2 mmol), $W(CO)_6$ (0.28 mmol), I_2 (7.1 mmol), K_2CO_3 (21.3 mmol), CH_2Cl_2 (40 mL), room temperature, pressure 80 atm, 15 h.

CHAPTER 4
CATALYTIC OXIDATIVE CARBONYLATION OF PRIMARY AND SECONDARY ∝,ω-DIAMINES TO CYCLIC UREAS

Cyclic Ureas

Cyclic ureas have interesting pharmacological properties which have lead to their use as inhibitors of a broad set of retroviral proteases, including HIV protease.[31] In addition, they have also found use as chiral auxiliaries for asymmetric synthesis.[32]

Several synthetic routes from diamines to the corresponding cyclic ureas have been described.[23] Most of these rely on nucleophilic reactions of the amines with phosgene and related compounds. Methods that convert primary diamines to the corresponding cyclic ureas have been reported for phosgene,[33] phosgene derivatives,[34] dialkyl carbonates,[35] carbonyl sulfide,[36] carbonyl selenide[37] and urea.[32] Due to the facile closure of five-membered rings, the conversion of ethylenediamine to 2-imidazolidinone has been a test case for these methods. Phosgene itself is ineffective for this substrate, producing the 5-membered cyclic urea in only 13% yield.[38] However, when the related aromatic phenylenediamine is reacted with phosgene, the cyclic urea is produced in a 50% yield.[33b] Phosgene derivatives, such as S,S-dimethyl dithiocarbonate, can be used to carbonylate ethylenediamine to the five-membered cyclic urea in 80% yield.[34] Furthermore, disuccinimido carbonate (DSC) serves to carbonylate ethylenediamine to 2-imidazolidinone in a 90% yield.[35] Urea itself can be transaminated in the presence of water at 200 °C to produce five-membered cyclic ureas from the corresponding diamines in about 85% yield.[32]

While there are several synthetic routes to prepare the parent cyclic ureas directly from primary diamines, the general difficulties associated with synthesis of tetrasubstituted ureas[24] render direct synthesis of N,N'-disubstituted cyclic ureas from secondary diamines more challenging. As a result, N,N'-disubstituted cyclic ureas are often prepared by deprotonation and alkylation of their unsubstituted analogues.[39]

Catalytic oxidative carbonylation of diamine substrates would provide an alternative route to cyclic ureas in which CO could be used as the carbonyl source. Oxidative carbonylation of primary amines to acyclic ureas has been reported to be catalyzed by complexes of Ni,[5a] Co,[5c] W,[40] Mn,[5e-f] Ru,[5g] and Pd.[5d,h,19] However, the transition metal-catalyzed reactions generally require high temperatures and pressures and yields tend to be much less for aliphatic amines than for aromatic ones. Main group elements such as sulfur[28] and selenium[29] can also serve as catalysts.

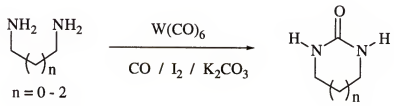
The formation of cyclic ureas by catalytic carbonylation has been much less well explored than the acyclic cases. Catalytic carbonylation of diamines with carbon monoxide to form cyclic ureas in high yields has been reported to proceed in the presence of elemental selenium, however the reaction generates hydrogen selenide as a byproduct and certain substrates such as 2-(2-aminoethylaniline) only form the cyclic urea in the presence of stoichiometric or excess selenium.[29] In a related process, carbonylation of both primary and secondary diamines to cyclic ureas using CO_2 as the carbonyl source and Ph_3SbO/P_4S_{10} as catalyst proceeds in moderate to good yields.[41] Prior reports of transition metal-catalyzed carbonylation of diamines cite cyclic ureas only as very minor or side products. As an example, $Mn_2(CO)_{10}$-catalyzed carbonylation of the diamines $H_2N(CH_2)_nNH_2$ (n = 2-4,6) yielded no cyclic products when n = 2,4,6 and only 6% of the six-membered urea when n = 3.[5f] Carbonylation of ethylenediamine catalyzed by $Ni(CO)_4$ yielded 2-imidazolidinone as a minor product in 10% yield.[42]

Based on the carbonylation chemistry developed with both **5** and $W(CO)_6$, it seemed feasible that the $W(CO)_6/I_2$ carbonylation system could be extended to include both

primary and secondary diamines. Under high dilution conditions, diamines could possibly be carbonylated to cyclic ureas. In addition, with this reaction, secondary diamines could be directly converted to N,N'-disubstituted cyclic ureas.

Catalytic Carbonylation of Primary Diamines to Cyclic Ureas

When the primary diamines $H_2NCH_2(CH_2)_nCH_2NH_2$ (n = 0 - 2) were reacted with CO (100 atm) in the presence of catalytic amounts of $W(CO)_6$ and nearly stoichiometric I_2, the diamines were converted to the corresponding cyclic ureas (eq 4.1). Note that the reactions were run at room temperature, in contrast to the 100 - 200° C ranges that are typical for catalytic oxidative carbonylation. The yields are significantly improved by addition of excess K_2CO_3 to scavenge the byproduct HI. Because the competitive formation of oligomers[19] is favored by high concentrations of diamine, it was necessary to employ high dilution conditions.

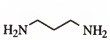
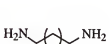


(4.1)

The results for a series of primary diamines are shown in **Table 4.1**. Preparation of the five, six and seven-membered cyclic ureas was achieved in moderate to good yields. The highest isolated yield was obtained for the 6-membered cyclic urea, while only trace amounts of the eight-membered ring compound could be detected in the reaction mixtures. Failure to close the eight-membered ring was not surprising as there are no reports in the literature of preparation of the compound directly from 1,5-pentanediamine. In addition, (+)-(1R,2R)-1,2-diphenyl-1,2-ethanediamine was carbonylated to the chiral 2-imidazolidinone in a 46% yield. All of the product cyclic ureas are known compounds and

they were characterized by comparison to authentic samples purchased from Aldrich or by comparison of their spectral data to literature values.

Table 4.1. Catalytic Carbonylation of Primary α,ω-Diamines to Cyclic Ureas.

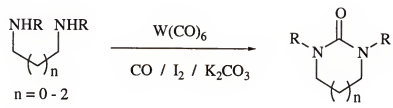
Diamine	Urea	Yield[a]
		40%
		51%
		38%
		trace
		46%

[a]Isolated yield per equivalent of starting diamine.

Catalytic Carbonylation of Secondary Diamines to Cyclic Ureas

Reaction of secondary diamines under similar catalytic oxidative carbonylation conditions resulted in conversion of the diamines to the corresponding N,N'-disubstituted

cyclic ureas (eq 4.2). Once again it was necessary to employ high dilution conditions to minimize formation of oligomers. The results for a series of secondary diamines are shown in **Table 4.2**.



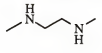
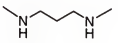
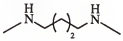
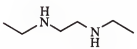
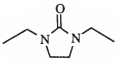
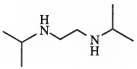
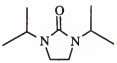
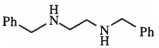
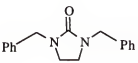
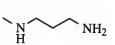
(4.2)

Closure of the diamines $CH_3NHCH_2(CH_2)_nCH_2NHCH_3$ (n = 0 - 2) to the corresponding five-, six-, and seven-membered cyclic ureas was achieved. The highest isolated yield (52%) was obtained for the six-membered ring. Note that the yields for closure of the N,N'-dimethyldiamines are comparable to those of their primary counterparts. In addition, pure material of the N,N'-dialkyl compounds in **Table 4.2** can be obtained by chromatography in contrast to the parent cyclic ureas of **Table 4.1** which were purified by sublimation due to their insolubility.

To probe steric limitations on the ring closure reaction, N,N'-diethyl, diisopropyl, and dibenzyl diamines were reacted under the standard conditions. The N,N'-disubstituted cyclic ureas were formed in varying yields, as seen in **Table 4.2**. As expected, 1,3-diethyl-2-imidazolidinone was produced in a 46% yield, similar to the yield of 1,3-dimethyl-2-imidazolidinone. Changing the substituents to benzyl groups dropped the yield only slightly. However, the steric hindrance of the bulky isopropyl groups dramatically reduced the yield of 1,3-diisopropyl-2-imidazolidinone to only 10%. Attempts to increase yields of the diisopropyl cyclic urea by raising the reaction temperature to 90 °C did not result in meaningful improvement (13% vs. 10% at room temperature). In a test case with one primary and one secondary amine terminus, N-methylpropanediamine reacted under the oxidative carbonylation conditions to produce the corresponding N-methyl cyclic urea in 31% yield, indicating that cyclization can compete with acyclic urea formation through

the more reactive primary amines. Once again, all of the products listed in **Table 4.2** are known compounds and were characterized by comparison to authentic samples purchased from Aldrich or by comparison to literature data.

Table 4.2 Catalytic Carbonylation of Secondary α,ω-Diamines to Cyclic Ureas.

Diamine	Urea	Yield[a]
		48%
		52%
		36%
		46%
		10%
		31%
		31%

[a]Isolated yield per equivalent of starting diamine.

The diamines in **Table 4.1** and **Table 4.2** lack functionality because they are simple cases intended to illustrate the ring closure. In conjunction with other studies of the oxidative carbonylation of primary amines to acyclic ureas under similar reaction conditions, extensive studies of functional group compatibility has been conducted.[43] The oxidative carbonylation reaction is tolerant of a wide variety of functionality, including groups such as aromatic amines, alcohols and halides.

The moderate yields of cyclic products can be attributed to competition of the ring closure reaction with the formation of acyclic oligomers. This problem has also been reported for the reactions of the phosgene equivalents with diamines.[32c] The initial crude yields of material derived from oxidative carbonylation of the diamines are approximately 85-90%. However, purification results in loss of approximately 50% of the crude product. Depending on the method of purification, the remaining material is left behind as residue in the sublimator or adheres to the top of the column during chromatography. These properties are consistent with formation of oligomeric ureas. Attempts to minimize the amount of oligomerization by further diluting the reaction mixtures merely slowed the reaction, rather than increasing the yields of the cyclic ureas. Further increasing the concentration of the reaction mixtures led to decreased yields of the cyclic ureas, while increasing the yields of the residue.

Summary and Conclusions

In conclusion, a simple method to catalytically convert α,ω-diamines and carbon monoxide to cyclic ureas at room temperature in moderate yields using $W(CO)_6$ as the catalyst has been developed. The catalyst is commercially available, inexpensive and air-stable. This is first known example of a transition metal-catalyzed procedure in which both primary and secondary diamines can serve as substrates. In the cases of the primary diamines, the yields of this catalytic carbonylation reaction are lower than those from some

of the methods that utilize phosgene derivatives. The yields from secondary diamines are more favorable because the direct conversion to the N,N'-disubstituted cyclic ureas by this method can be compared to multistep sequences in which conversion of the primary diamine to the corresponding cyclic urea is followed by deprotonation and alkylation. Such a sequence for preparation of protease inhibitors is described in reference 39. The simplicity of this method, the direct conversion of secondary diamines to N,N'-disubstituted cyclic ureas, and the functional group tolerance are appealing features of this carbonylation reaction.

CHAPTER 5
EXPERIMENTALS

Experimental Procedures

General

Standard inert atmosphere Schlenk, cannula, and glove box techniques and freshly distilled solvents were used in all experiments unless stated otherwise. Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone. Methylene chloride, and hexane were distilled over calcium hydride. All NMR solvents were degassed by 3 freeze-pump-thaw cycles, then stored in an inert-atmosphere glove box over 3 Å molecular sieves. All other chemicals were purchased in reagent grade and used with no further purification unless stated otherwise.

Authentic samples of the formamides were purchased from Aldrich. Authentic samples of the ureas were prepared from the corresponding amines and isocyanates[2] or were purchased from Aldrich. $[W(NPh)I_2(CO)_2]_2$ (**5**), [18] $W(NPh)I_2CO)_2(CH_3CN)$ (**7**),[18] $W(NPh)Br_2(CO)_2(CH_3CN)$ (**18a**),[22] and $W(NPh)Cl_2(CO)_2(CH_3CN)$ (**18b**)[22] were synthesized according to the literature methods.

^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer. IR spectra were recorded on a Perkin-Elmer 1600 FTIR. GC was performed on an HP5890 chromatograph containing a 30 m x 0.75 mm column of SPB-20 on fused silica or a 15 m x 0.32 mm column of AT-WAX on fused silica. High-resolution mass spectrometry was performed by the University of Florida analytical service.

Stoichiometric Carbonylation of Secondary Amines with **5**

The following procedure is typical: To a stirred solution of dimer **5** (100 mg, 0.086 mmol) in 5 mL of CH_2Cl_2 was added 10 equiv of piperidine (73 mg, 0.86 mmol). A color change from red to purple occurred immediately. The solution was stirred under N_2 for 30 min, then opened to air for 24 hr, during which the solution slowly turned from purple to yellow. The solution was then filtered through a small pad of Celite. The organic product was identified as 1-formylpiperidine by comparison to an authentic sample. Its yield was determined by GC analysis, based on a standard calibration curve, of the solution to be 7 mg (36% yield).

Stoichiometric Carbonylation of Primary Amines with **5**

The following procedure is typical: To a stirred solution of dimer **5** (110mg, 0.095 mmol) in 5 mL of CH_2Cl_2 was added 10 equiv of aniline (0.086 mL, 0.95 mmol). A color change from red to purple occurred immediately. The solution was stirred under N_2 for 30 minutes, then opened to air for 24 hr, during which the solution slowly turned from purple to dark orange and a white solid precipitated out. The precipitate was collected and rinsed with 2 x 10 mL of CH_2Cl_2 to obtain a white solid (42.3 mg, 105%). The solid was identified as diphenyl urea by comparison to an authentic sample.

Stoichiometric Carbonylation of α,ω-Diamines with **5**

The following procedure is typical: To a stirred solution of dimer **5** (110 mg, 0.094 mmol) in 50 mL of CH_2Cl_2 was added 6 eq of 1,3-diaminopropane (0.062 mL, 0.75 mmol). The solution immediately became green and cloudy. The solution was stirred under N_2 for 30 minutes, then opened to air for 24 h, during which the solution became

colorless and a yellow solid precipitated. The solution was separated from the precipitate, and the precipitate was rinsed with 10 mL boiling CH_2Cl_2 and 10 mL boiling THF. The rinsings were combined with the clear solution. The clear solution was concentrated and successively rinsed with 20 mL hexane and 20 mL ether to obtain a white solid (13 mg, 68% yield). The solid was identified as tetrahydro-2-pyrimidone by comparison with an authentic sample.

Synthesis of $(CO)_2I_2W(NPh)(H_2NCH_2CH_2CH_2CH_3)$ (**11a**)

To a stirred solution of dimer **5** (77 mg, 0.066 mmol) in 20 mL of CH_2Cl_2 was added 2 equiv of *n*-butylamine (0.013 mL, 0.13 mmol). A color change from red to purple occurred immediately. After 1 hr of stirring the CH_2Cl_2 was removed under vacuum. The red oil was redissolved in 2 mL of CH_2Cl_2 and 5 mL of hexane was layered on top. The solution was placed in a -40°C freezer overnight. The red solution was cannulated away from any precipitate and concentrated. The resulting red oil was collected into 50 mL of ether and cannulated away from any insoluble particles. The solvent was removed under vacuum to yield **11a** as a red oil (11 mg, 13% yield). IR (CH_2Cl_2): ν_{CO} 2066, 1988 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.50-7.21 (m, 5H), 4.33 (s, 1H), 4.02 (s, 1H), 3.37 (m, 2H), 1.68 (m, 2H), 1.44 (m, 2H), 0.98 (t, 3H). ^{13}C NMR ($CDCl_3$): δ 208.6, 208.5, 153.3, 129.5, 129.1, 124.9, 51.9, 34.6, 19.5, 13.4. HRMS (FAB): 629.886 $(M\text{-}CO)^+$, calcd: 629.8824

Synthesis of $(CO)_2I_2W(NPh)(H_2NCH_2CH_2CH_3)$ (**11b**)

To a stirred solution of dimer **5** (53 mg, 0.045 mmol) in 20 mL of CH_2Cl_2 was added 2 equiv of *n*-propylamine (0.0075 mL, 0.091 mmol). A color change from red to purple occurred immediately. After 1 hr of stirring the CH_2Cl_2 was removed under

vacuum. The red oil was redissolved in 2 mL of CH_2Cl_2 and 5 mL of hexane was layered on top. The solution was placed in a -40°C freezer overnight. The red solution was cannulated away from any precipitate and concentrated. The resulting red oil was taken up into 50 mL of ether and cannulated away from any insoluble particles. The solvent was removed under vacuum to yield **11b** as a red oil (53 mg, 63% yield). IR (CH_2Cl_2): ν_{CO} 2067, 1988 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.50-7.26 (m, 5H), 4.35 (s, 1H), 4.03 (s, 1H), 3.34 (m, 2H), 1.75 (m, 2H), 1.04 (t, 3H). ^{13}C NMR ($CDCl_3$): δ 208.5, 208.4, 153.8, 129.4, 129.1, 124.9, 53.8, 25.8, 10.6.

Synthesis of $(CO)_2I_2W(NPh)(H_2NC(CH_3)_3)$ (**11c**)

To a stirred solution of dimer **5** (113 mg, 0.097 mmol) in 20 mL of CH_2Cl_2 was added 2 equiv of *t*-butylamine (0.020 mL, 0.195 mmol). A color change from red to purple occurred immediately. After 2 hr of stirring the CH_2Cl_2 was removed under vacuum. The purple oil was redissolved in 2 mL of CH_2Cl_2 and 5 mL of hexane was layered on top. The solution was placed in a -40°C freezer overnight. The red solution was cannulated away from any precipitate and concentrated. The resulting red solid was taken up into 50 mL of hexane and cannulated away from any insoluble particles. The solvent was removed under vacuum to yield **11c** as a red solid (45 mg, 70% yield). IR (CH_2Cl_2): ν_{CO} 2067, 1987 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.49-7.18 (m, 5H), 4.83 (d, 1H), 4.07 (d, 1H), 1.44 (t, 9H). ^{13}C NMR ($CDCl_3$): δ 210.3, 207.5, 153.3, 129.5, 129.2, 124.9, 55.8, 30.8. HRMS (FAB): 629.886 $(M\text{-}CO)^+$, calcd: 629.8824.

Synthesis of $(CO)_2I_2W(NPh)(pip)$ (**12**)

To a stirred solution of dimer **5** (170 mg, 0.146 mmol) in 15 mL of CH_2Cl_2 was added 2 equiv of piperidine (0.028 mL, 0.292 mmol). A color change from red to purple occurred immediately. After stirring for 5 min, the CH_2Cl_2 was removed under vacuum. The resulting oil was taken up in 10 mL of Et_2O and cannulated away from any insoluble particles. Hexane (5 mL) was added and the solution was placed in a -40 °C freezer overnight. Complex **12** was collected as a dark purple powder (162 mg, 83% yield). X-ray quality crystals were grown from a 50:50 mixture of Et_2O and hexane. ^1H NMR ($CDCl_3$) δ 7.4-7.1 (m, 5H), 4.33 (s, 1H), 3.15 (q, 2 H), 2.75 (q, 2H), 1.87-1.47 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 209.8, 207.8, 153.2, 129.6, 129.1, 125.1, 59.1, 56.7, 28.9, 28.8, 23.1. IR (CH_2Cl_2) ν_{CO} 2066, 1987 cm^{-1}. HRMS (FAB): 641.9025 $(M - CO)^+$, calcd: 641.9175.

Crystal Structure of **12**

Data were collected at 173 K on a Siemens SMART PLATFORM equipped with a CCD area detector and a graphite monochromator utilizing MoK_α radiation (λ = 0.71073 Å). Cell parameters were refined using up to 8192 reflections. A hemisphere of data (1381 frames) was collected using the ω-scan method (0.3° frame width). The first 50 frames were remeasured at the end of data collection to monitor instrument and crystal stability (maximum correction on I was < 1 %). Psi scan absorption corrections were applied based on the entire data set.

The structure was solved by the Direct Methods in *SHELXTL5*[44] and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms. 182 parameters were refined in the final cycle of refinement using 3526

reflections with $I > 2\sigma(I)$ to yield R_1 2.29% and wR_2 of 4.83%, respectively. Refinement was done using F^2.

Synthesis of [(CO)$_2$IW(NPh)(H$_2$NCH$_2$CH$_2$CH$_2$CH$_3$)$_2$]I (**13a**)

To a stirred solution of dimer **5** (100 mg, 0.086 mmol) in 20 mL of CH_2Cl_2 was added 4 equiv of *n*-butylamine (0.034 mL, 0.34 mmol) at 0°C. A color change from red to maroon occurred immediately. After 2 hr of stirring, the CH_2Cl_2 was removed under vacuum. The red oil was redissolved in 2 mL of CH_2Cl_2 and 25 mL of ether was added. The solution was placed in a -40°C freezer for 2 days. The resulting orange powder (**13a**) was isolated by filtration (43 mg, 40% yield). IR (CH_2Cl_2): ν_{CO}, 2060, 1989 cm^{-1}. ^{1}H NMR (CD_2Cl_2): δ 7.28 (m, 3H), 7.04 (d, 2H), 5.35 (s, 2H), 4.88 (s, 2H), 3.15 (m, 4H), 1.85 (m, 4H), 1.41 (m, 4H), 0.91 (t, 6H). ^{13}C NMR (CD_2Cl_2): δ 214.7, 154.5, 129.3, 127.5, 127.3, 50.1, 34.3, 20.5, 13.8.

Synthesis of [(CO)$_2$IW(NPh)(H$_2$NCH$_2$CH$_2$CH$_3$)$_2$]I (**13b**)

To a stirred solution of dimer **5** (111 mg, 0.094 mmol) in 25 mL of CH_2Cl_2 was added 8 equiv of *n*-propylamine (0.062 mL, 0.75 mmol) at 0°C. A color change from red to maroon occurred immediately. After 1 hr of stirring, the CH_2Cl_2 was removed under vacuum. The red oil was redissolved in 2 mL of CH_2Cl_2 and 25 mL of ether was added. The solution was placed in a -40°C freezer for 2 days. The resulting orange powder (**13b**) was isolated by filtration (30 mg, 26% yield). IR (CH_2Cl_2): ν_{CO}, 2060, 1989 cm^{-1}. ^{1}H NMR (CD_2Cl_2): δ 7.29 (m, 3H), 7.06 (d, 2H), 5.32 (s, 2H), 4.88 (s, 2H), 3.08 (m, 4H),

1.92 (m, 4H), 0.98 (t, 6H). ^{13}C NMR (CD_2Cl_2): δ 214.7, 154.5, 129.3, 127.5, 127.4, 52.1, 25.8, 11.6.

Catalytic Carbonylation of Primary Amines with **5** (Solid Oxidants)

The following procedure is typical: To a stirred solution of dimer **5** (260 mg, 0.22 mmol) in 30 mL of CH_2Cl_2 was added 100 equiv of *n*-butylamine (2.2 mL, 22 mmol). A color change from red to deep purple occurred immediately. The solution was stirred under N_2 for 20 min, then added to a Parr high-pressure vessel, followed by addition of iodosylbenzene (4.9 g, 22 mmol). The vessel was then charged with 100 atm of CO, and left to stir under pressure for 24 h. The pressure was released and the lemon yellow solution was then filtered through Celite and concentrated. The resulting yellow solid was dissolved in ethyl acetate and chromatographed on silica with ethyl acetate as eluent to obtain a white solid (616 mg, 3.59 mmol, 12 turnovers per equiv of dimer **5**) The solid was identified as di-*n*-butylurea by comparison with an authentic sample.

Catalytic Carbonylation of Primary Amines with **5** (Air Oxidant)

Caution! High pressure mixtures of CO and O_2 are explosive under certain conditions. To a stirred solution of dimer **5** (278 mg, 0.24 mmol) in 50 mL of CH_2Cl_2 was added 300 equiv of *n*-butylamine (7.3 mL, 71 mmol). A color change from red to deep purple occurred immediately. The solution was stirred under N_2 for 20 min, then added to a Parr high-pressure vessel. The vessel was then charged with 800 psi of CO, followed by 200 psi of air, and left to stir under pressure for 24 h. The pressure was released and the pale yellow solution was then filtered through Celite and concentrated. The resulting yellow oil was dissolved in ethyl acetate and chromatographed on silica with ethyl acetate as eluent to obtain a white solid (49 mg, 0.28 mmol, 1.2 turnovers per equiv

of dimer **5**). The solid was identified as di-*n*-butylurea by comparison with an authentic sample.

Catalytic Carbonylation of Primary Amines with $W(CO)_6$

The following procedure is typical: To a stirred solution of $W(CO)_6$ (75 mg, 0.21 mmol) in 25 mL of CH_2Cl_2 in the glass liner of a Parr high-pressure vessel was added 100 equiv of *n*-butylamine (2.1 mL, 21 mmol), K_2CO_3 (3.52 g, 21 mmol) and 50 equiv of iodine (2.56 g, 10.5 mmol). The vessel was then charged with 100 atm of CO, and left to stir under pressure for 24 h. The pressure was released and the maroon solution was filtered and then rinsed with a Na_2SO_3 solution. The resulting pale yellow solution was then dried with $MgSO_4$ and filtered. The solution was concentrated to yield a pale yellow solid, which was then rinsed with 25 mL hexane. The solid was then taken up in 25 mL ether, and filtered to remove any residual $W(CO)_6$. The ether solution was concentrated to obtain a white solid (1.4 g, 8.1 mmol, 39 turnovers per equiv of tungsten) The solid was identified as di-*n*-butylurea by comparison with an authentic sample.

Catalytic Carbonylation of Secondary Amines with $W(CO)_6$

The following procedure is typical: To a stirred solution of $W(CO)_6$ (100 mg, 0.28 mmol) in 40 mL of CH_2Cl_2 in the glass liner of a Parr high-pressure vessel was added 50 equiv of piperidine (1.4 mL, 14 mmol), K_2CO_3 (1.95 g, 14.2 mmol) and 25 equiv of iodine (1.8 g, 7.1 mmol). The vessel was then charged with 100 atm of CO, and left to stir under pressure for 24 h. The pressure was released and the maroon solution was filtered and then rinsed with a Na_2SO_3 solution and 1M HCl. The resulting pale red solution was then dried with $MgSO_4$ and filtered. The solution was concentrated to yield a red oil. The resulting red oil was dissolved in ethyl acetate and chromatographed on silica with ethyl

acetate as eluent to obtain a colorless oil. (0.47g, 36% yield). The liquid was identified as dipiperidylurea by comparison with an authentic sample.

Catalytic Carbonylation of Primary Diamines with $W(CO)_6$

The following procedure is typical: To a stirred solution of $W(CO)_6$ (30 mg, 0.085 mmol) in a 90 mL solution of CH_2Cl_2 in the glass liner of a Parr high-pressure vessel was added 100 equiv of ethylenediamine (0.57 mL, 8.54 mmol), 210 equiv K_2CO_3 (2.47 g, 17.93 mmol) and 90 equiv of iodine (1.95 g, 7.68 mmol). The vessel was then charged with 100 atm of CO, and left to stir under pressure at room temperature for 24 h. The pressure was released and the maroon solution was filtered away from a red solid. The CH_2Cl_2 layer was concentrated and then taken up into methanol, while the red solid was rinsed with methanol. Both methanol fractions were combined, and concentrated to obtain a yellow powder. The yellow powder was then sublimed to obtain a white solid (0.29g, 40% yield). The solid was identified as 2-imidazolidone by comparison with an authentic sample.

Catalytic Carbonylation of Secondary Diamines with $W(CO)_6$

The following procedure is typical: To a stirred solution of $W(CO)_6$ (30 mg, 0.085 mmol) in 90 mL of CH_2Cl_2 in the glass liner of a Parr high-pressure vessel was added 150 equiv of N,N'-dimethylethylenediamine (1.36 mL, 12.8 mmol), 310 equiv K_2CO_3 (3.63 g, 26.3 mmol) and 140 equiv of iodine (3.02 g, 11.9 mmol). The vessel was then charged with 100 atm of CO, and left to stir under pressure at room temperature for 24 h. The pressure was released and the yellow solution was filtered away from a white solid and concentrated. The resulting pale yellow oil was dissolved in ethyl acetate and chromatographed on silica with ethyl acetate as eluent to obtain a colorless liquid (0.68g,

47% yield). The liquid was identified as 1,3-dimethyl-2-imidazolidone by comparison with an authentic sample.

APPENDIX
CRYSTAL DATA AND STRUCTURE REFINEMENT FOR **12**

Table A.1 Crystal data and structure refinement for **12**.

Empirical formula	$C_{13}\ H_{16}\ I_2\ N_2\ O_2\ W$
Formula weight	669.93
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 8.9583(3) Å a = 90° b = 20.6165(5) Å b = 103.22° c = 10.0082(3) Å g = 90°
Volume, Z	1799.41(9) A^3, 4
Density (calculated)	2.473 Mg/m^3
Absorption coefficient	9.853 mm^{-1}
F(000)	1216
Crystal size	0.06 x 0.11 x 0.21 mm
Theta range for data collection	1.98 to 27.50°
Limiting indices	$-11 \le h \le 12$, $-24 \le k \le 27$, $-11 \le l \le 13$
Reflections collected	12134
Independent reflections	4105 [R(int) = 0.0284]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4099 / 0 / 182

Goodness-of-fit on F^2	1.010
Final R indices [I>2sigma(I)]	R_1 = 0.0229, wR_2 = 0.0483 [3526]
R indices (all data)	R_1 = 0.0312, wR_2 = 0.0514
Extinction coefficient	0.00067(6)
Largest diff. peak and hole	1.359 and -0.843 e.A^3

Table A.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **12**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
W	13750(1)	8819(1)	7462(1)	25(1)
I1	16676(1)	9364(1)	7537(1)	35(1)
I2	14232(1)	8950(1)	10308(1)	35(1)
O12	15533(4)	7476(2)	7969(4)	52(1)
O13	13757(5)	8777(2)	4296(4)	62(1)
N1	12777(3)	9826(2)	7441(3)	26(1)
N2	12049(4)	8359(2)	7018(4)	28(1)
C1	11168(4)	9817(2)	7669(5)	37(1)
C2	10576(5)	10500(2)	7845(6)	45(1)
C3	10637(5)	10928(2)	6634(5)	45(1)
C4	12259(5)	10935(2)	6379(5)	43(1)
C5	12823(5)	10248(2)	6232(5)	36(1)
C6	10920(4)	7909(2)	6451(4)	25(1)
C7	11291(5)	7365(2)	5775(5)	39(1)
C8	10159(5)	6927(2)	5222(5)	43(1)
C9	8672(5)	7020(2)	5338(5)	41(1)
C10	8299(5)	7564(2)	5998(5)	42(1)
C11	9418(4)	8012(2)	6577(5)	33(1)
C12	14934(5)	7959(2)	7777(5)	34(1)
C13	13783(5)	8813(2)	5435(5)	39(1)

Table A.3 Bond lengths [Å] and angles [°] for **12**.

W-N2	1.764(3)
W-C13	2.036(5)
W-C12	2.053(4)
W-N1	2.249(3)
W-I2	2.7941(3)
W-I1	2.8359(3)
O12-C12	1.128(5)
O13-C13	1.138(6)
N1-C5	1.499(5)
N1-C1	1.511(5)
N1-H1	0.93
N2-C6	1.394(5)
C1-C2	1.528(5)
C1-H1A	0.99
C1-H1B	0.99
C2-C3	1.511(7)
C2-H2A	0.99
C2-H2B	0.99
C3-C4	1.531(7)
C3-H3A	0.99
C3-H3B	0.99
C4-C5	1.521(6)
C4-H4A	0.99
C4-H4B	0.99
C5-H5A	0.99
C5-H5B	0.99
C6-C7	1.389(5)
C6-C11	1.395(5)
C7-C8	1.376(6)
C7-H7	0.95
C8-C9	1.377(6)
C8-H8	0.95
C9-C10	1.383(6)
C9-H9	0.95
C10-C11	1.388(6)
C10-H10	0.95
C11-H11	0.95
N2-W-C13	87.4(2)
N2-W-C12	87.7(2)
C13-W-C12	91.3(2)
N2-W-N1	100.59(12)
C13-W-N1	95.2(2)
C12-W-N1	169.7(2)
N2-W-I2	103.39(11)
C13-W-I2	169.21(13)
C12-W-I2	88.44(13)
N1-W-I2	83.68(9)
N2-W-I1	163.63(10)
C13-W-I1	78.75(13)
C12-W-I1	84.03(11)

N1-W-I1	89.36(8)
I2-W-I1	90.501(10)
C5-N1-C1	109.4(3)
C5-N1-W	117.5(2)
C1-N1-W	111.7(2)
C5-N1-H1	105.8(2)
C1-N1-H1	105.8(2)
W-N1-H1	105.81(8)
C6-N2-W	164.9(3)
N1-C1-C2	112.0(3)
N1-C1-H1A	109.2(2)
C2-C1-H1A	109.2(3)
N1-C1-H1B	109.2(2)
C2-C1-H1B	109.2(3)
H1A-C1-H1B	107.9
C3-C2-C1	111.7(4)
C3-C2-H2A	109.3(2)
C1-C2-H2A	109.3(2)
C3-C2-H2B	109.3(2)
C1-C2-H2B	109.3(3)
H2A-C2-H2B	107.9
C2-C3-C4	110.4(4)
C2-C3-H3A	109.6(2)
C4-C3-H3A	109.6(2)
C2-C3-H3B	109.6(3)
C4-C3-H3B	109.6(3)
H3A-C3-H3B	108.1
C5-C4-C3	110.9(4)
C5-C4-H4A	109.5(3)
C3-C4-H4A	109.5(3)
C5-C4-H4B	109.5(2)
C3-C4-H4B	109.5(3)
H4A-C4-H4B	108.0
N1-C5-C4	113.1(4)
N1-C5-H5A	109.0(2)
C4-C5-H5A	109.0(3)
N1-C5-H5B	109.0(2)
C4-C5-H5B	109.0(2)
H5A-C5-H5B	107.8
C7-C6-N2	120.2(3)
C7-C6-C11	120.7(4)
N2-C6-C11	119.1(3)
C8-C7-C6	119.3(4)
C8-C7-H7	120.4(3)
C6-C7-H7	120.4(2)
C7-C8-C9	120.9(4)
C7-C8-H8	119.5(3)
C9-C8-H8	119.5(3)
C8-C9-C10	119.8(4)
C8-C9-H9	120.1(3)
C10-C9-H9	120.1(3)
C9-C10-C11	120.6(4)
C9-C10-H10	119.7(3)
C11-C10-H10	119.7(2)

C10-C11-C6	118.7(4)
C10-C11-H11	120.6(2)
C6-C11-H11	120.6(2)
O12-C12-W	177.1(4)
O13-C13-W	176.1(4)

Symmetry transformations used to generate equivalent atoms:

Table A.4 Anisotropic displacement parameters ($A^2 \times 10^3$) for **12**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U11 + 2 h k a^* b^* U12]$

	U11	U22	U33	U23	U13	U12
W	24(1)	22(1)	29(1)	-2(1)	3(1)	-1(1)
I1	26(1)	32(1)	48(1)	1(1)	12(1)	-1(1)
I2	40(1)	34(1)	28(1)	2(1)	3(1)	-10(1)
O12	43(2)	34(2)	72(3)	-1(2)	-1(2)	9(2)
O13	78(3)	72(3)	36(2)	-10(2)	16(2)	-3(2)
N1	26(2)	23(2)	28(2)	-2(1)	4(1)	-2(1)
N2	27(2)	24(2)	32(2)	-3(1)	5(1)	2(1)
C1	28(2)	28(2)	55(3)	-3(2)	10(2)	-1(2)
C2	38(2)	31(2)	66(4)	-8(2)	13(2)	5(2)
C3	42(3)	31(2)	51(3)	-10(2)	-11(2)	8(2)
C4	44(3)	30(2)	47(3)	10(2)	-6(2)	1(2)
C5	38(2)	36(2)	33(2)	9(2)	4(2)	5(2)
C6	25(2)	24(2)	25(2)	0(2)	2(2)	2(1)
C7	31(2)	35(2)	50(3)	-12(2)	7(2)	-1(2)
C8	48(3)	30(2)	48(3)	-15(2)	0(2)	-3(2)
C9	38(2)	31(2)	47(3)	2(2)	-6(2)	-13(2)
C10	24(2)	49(3)	52(3)	5(2)	5(2)	0(2)
C11	28(2)	34(2)	38(3)	-5(2)	8(2)	4(2)
C12	29(2)	29(2)	41(3)	0(2)	0(2)	0(2)
C13	39(2)	35(2)	41(3)	-3(2)	7(2)	1(2)

Table A.5 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **12**.

	x	y	z	U(eq)
H1	13374(3)	10036(2)	8200(3)	31
H1A	11153(4)	9558(2)	8499(5)	44
H1B	10475(4)	9605(2)	6877(5)	44
H2A	9505(5)	10473(2)	7947(6)	54
H2B	11204(5)	10696(2)	8692(6)	54
H3A	10332(5)	11375(2)	6815(5)	54
H3B	9906(5)	10766(2)	5805(5)	54
H4A	12260(5)	11183(2)	5532(5)	51
H4B	12964(5)	11153(2)	7154(5)	51
H5A	12181(5)	10050(2)	5394(5)	43
H5B	13889(5)	10268(2)	6113(5)	43
H7	12316(5)	7296(2)	5696(5)	47
H8	10407(5)	6556(2)	4753(5)	52
H9	7904(5)	6710(2)	4965(5)	50
H10	7267(5)	7633(2)	6056(5)	51
H11	9167(4)	8381(2)	7050(5)	40

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BIOGRAPHICAL SKETCH

Jennifer Ellen McCusker was born on November 7, 1972, in Toms River, NJ. She spent most of her childhood playing in the waters and swamps along the Jersey Shore. As a child, she was interested in medicine because she was born with a Tetrology of Fallot. As a result, Jennifer spent the first seven years of her life in and out of Deborah Heart and Lung Center. Her desire to become a pediatric cardiovascular surgeon motivated her interest in biology. In high school, she did well in most subjects, except the two that she uses most today, chemistry and drivers education. In the fall of 1991 Jennifer entered the University of Richmond as a biology major. After deciding that she did not like sick people, she changed her major to chemistry. Her interest in chemistry grew in the labs of Dr. William Myers. She spent the summer of 1994 in laboratories of Dr. Ken Feldman at Pennsylvania State University conducting synthetic organic research. Jennifer graduated from the University of Richmond in 1995 and decided to immediately enroll in graduate school at the University of Florida. She joined the McElwee-White research group and spent four years working on carbonylation chemistry. During her graduate studies, she poisoned herself numerous times with carbon monoxide, made one trip to the emergency room, and constantly smelled like cat pee. In her spare time, Jennifer enjoys murder mystery novels, theatre, spending time with Steve, and playing with her 28 pound orange tabby, Miles. After completion of her Ph.D. in organic/organometallic chemistry Jennifer will head off to Eastman Chemical Company to work as an advanced research chemist.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August 1999

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